Obesity, Inflammation, and the Potential Application of Pharmaconutrition

ABSTRACT: Obesity is an emerging problem worldwide. Hospitalized obese patients often have a worse outcome than patients of normal weight, particularly in the setting of trauma and critical care. Obesity creates a low-grade systemic inflammatory response syndrome (SIRS) that is similar (but on a much smaller scale) to gram-negative sepsis. This process involves up-regulation of systemic immunity, is characterized clinically by insulin resistance and the metabolic syndrome, and puts the patient at increased risk for organ failure, infectious morbidity, and mortality. Through lipotoxicity and cytokine dysregulation, obesity may act to prime the immune system, predisposing to an exaggerated subsequent immune response when a second clinical insult occurs (such as trauma, burns, or myocardial infarction).

Specialized nutrition therapy for such patients currently consists of a hypocaloric, high-protein diet. However, this approach does not address the putative pathophysiologic mechanisms of inflammation and altered metabolism associated with obesity. A number of dietary agents such as arginine, fish oil, and carnitine may correct these problems at the molecular level. Pharmaconutrition formulas may provide exciting innovations for the nutrition therapy of the obese patient.

Impact of Obesity on Patient Outcome in Trauma and Critical Illness

In the obese critically ill patient, multiple associated comorbidities, such as diabetes, may increase risk in the ICU. With few exceptions, most reports in the literature indicate that obese patients have a more adverse outcome in a medical ICU compared with nonobese patients. Obesity critically ill patients tend to have a higher simplified acute physiologic score (SAP), are more likely to have depressed left ventricular function, and are at greater risk for multiple-organ failure (MOF) than the nonobese. Obese patients have been shown to have longer duration of mechanical ventilation (7.7 vs 4.6 days) and increased ICU length of stay (9.3 vs 5.8 days) compared with nonobese patients. Obese patients also had higher rates of ICU-acquired infections,
sepsis, and ventilator-associated pneumonia (VAP) than their nonobese counterparts. Not surprisingly, several studies have shown overall mortality to be significantly higher in obese (30%–32%) vs nonobese (17%–18%) ICU patients.

Similarly, the data suggesting more adverse outcome are even more compelling in obese trauma patients. In blunt (nonpenetrating) trauma, obesity has been shown to increase pulmonary infections, ICU length of stay (LOS), and mortality. Choban and colleagues reported a direct correlation between BMI and mortality. The mortality rate was 42% in obese trauma patients (BMI ≥31 kg/m²) compared with 8% in those patients who were overweight (BMI 27–31 kg/m²) and 5% in those who had normal weight (BMI ≤27 kg/m²). After controlling for factors such as age, diabetes, chronic obstructive pulmonary disease (COPD), and injury severity score (ISS), obese patients were shown to be 7.1 times more likely to die compared with nonobese patients. Obesity has been shown to affect the incidence of MOF in blunt force trauma patients as well. Obese trauma patients had a higher rate of MOF (37% vs 22%) than nonobese control patients. Obesity was independently associated with MOF when controlling for variables such as age and ISS. Additional findings from these trauma studies suggest that obese individuals have increased hospital LOS and infectious morbidity (bacteremia, urosepsis, and VAP) compared with nonobese controls.

Of interest is the observation that nutrition therapy, a critical component of ICU care, has not been independently investigated in any of these aforementioned ICU or trauma studies. In fact, specific evidence gleaned from the evaluation of enteral nutrition therapy in obese ICU patients is limited to a handful of inadequately controlled studies.

**Nutrition Therapy and Obesity**

The current gold standard of nutrition therapy for obese ICU patients includes enteral tube feedings that are high in protein and low in total calories. Previous studies evaluating parenteral feeding in obesity showed benefit from hypocaloric or hypenergetic diets. These diets contained nutrient mixtures characterized by a low calorie-to-nitrogen ratio, with an exaggerated provision of protein (up to 2 g per kg of ideal body weight per day). In 2002, Dickerson et al reported a study that evaluated hypocaloric enteral tube feeding in critically ill obese patients. Results showed improved outcome from this hypocaloric diet, with decreased ICU LOS and a trend toward reduced duration of mechanical ventilation compared with patients given a “eucaloric” diet. Combined, these studies suggest that critically ill obese patients given a hypocaloric diet either enterally or parenterally could achieve nitrogen balance despite ongoing weight loss. Furthermore, Choban and colleagues examined a combined database of hospitalized obese patients stratified by BMI. They found that higher BMI correlated with more negative nitrogen balance, hyperglycemia, and even mortality at a given level of dietary protein intake. Therefore, as the degree of obesity (BMI) increases, the dietary protein intake required to achieve nitrogen balance also increases (>2.5 g/kg ideal body weight [IBW]/d). Although these findings are a step in the right direction, the strategy of providing a high-protein hypocaloric diet for these patients does not address the key underlying pathologic process of obesity: chronic inflammation. Inflammation generated by obesity itself may be the link to the adverse health consequences that place these patients at increased risk in the ICU.

**Mechanisms of Obesity-Induced Inflammation and Organ Dysfunction**

Obesity causes inflammation and organ dysfunction through a variety of mechanisms that are becoming increasingly well defined. Understanding these mechanisms is important in order to identify molecular targets for nutrition intervention. Mechanistically, lipotoxicity is a critically important emerging concept. During lipotoxicity, a key factor of obesity-associated inflammation is adipokine dysregulation.

**Lipotoxicity**

A critical emerging concept is that of “good fat vs bad fat.” There is great variation between individuals in their ability to safely manage caloric excess. Not all obese patients develop the metabolic syndrome or other obesity-associated diseases. Some patients may gain weight but remain relatively healthy, whereas others lose weight but deteriorate from an overall health standpoint. For example, in a rodent model of obesity, weight loss with the popular dietary supplement conjugated linoleic acid (CLA) produces lipodystrophy, insulin resistance, and NAFLD. Ironically, these rodents have shown progression from a state of being relatively “fat and healthy” to a state of being “skinny and unhealthy.” Lipid management at the cellular level influences the degree to which disease processes and comorbidities develop in obesity. Adipogenesis may actually be a protective adaptation against caloric excess.

When caloric intake exceeds energy expenditure, excess calories will be stored as lipids. Both the location and type of lipid accumulation determine the presence or absence of obesity-related disease. All tissues have an inherent ability to store lipid. However, different tissues vary greatly in the quantity of lipid they can safely store. For example, adipose tissue has a much greater innate lipid storage capacity than other “ectopic” tissues, such as liver or muscle. When lipid accumulation exceeds this innate storage capacity, cellular and ultimately
organ dysfunction may ensue. This phenomenon has been called lipotoxicity. Experimentally, tissue-specific disease has been demonstrated to occur in the presence of excess lipid accumulation in the following organs: liver (NAFLD), pancreas (diabetes), muscle (insulin resistance), and heart (diabetic cardiomyopathy). Furthermore, there seems to be an organ-specific hierarchy for safe lipid storage. Peripheral (subcutaneous) adipose tissue is preferable to central (visceral) adipose tissue, which, in turn, is preferable to ectopic tissues such as the liver. However, it is becoming increasingly clear that even adipose tissue may be subject to lipotoxicity, with manifestations of adipokine dysregulation.

Although the amount and location of lipid storage are critical, perhaps the most important determinants of lipotoxicity are the specific type of lipid stored and how it is stored. Saturated free long-chain fatty acids (LCFA) seem to be the most plausible inducers of lipotoxicity, whereas monounsaturated (MUFA) and polyunsaturated fatty acids (PUFA) may be protective. Furthermore, esterification of LCFA into triglycerides appears to be a protective “sink,” or less toxic storage form for LCFA. In an animal model of NAFLD, disruption of triglyceride synthesis resulted in much more severe hepatic inflammation and fibrosis due to increased intracellular free fatty acids (FFAs).

There are a variety of intracellular and extracellular mechanisms responsible for lipotoxicity. These include adipokine dysregulation, apoptotic cell death (“lipoapoptosis”), oxidative stress, unfolded protein response (endoplasmic reticulum stress), mitochondrial dysfunction, endothelial dysfunction, and alterations in the trans-methylation or trans-sulfuration pathways. Intriguingly, many of these mechanisms are amenable to specialized nutrition therapy, apart from traditional weight loss diets. Each mechanism may have some degree of tissue specificity, as evidenced by the fact that an effective treatment for one organ may be potentially deleterious to another. For example, peroxisome-proliferator-activated receptor-γ (PPAR-γ) agonists (such as the oral hypoglycemic agent rosiglitazone) promote adipocyte proliferation and insulin sensitivity, while down-regulating the inflammatory response through inhibition of nuclear factor-κB (NFκB) activation. Likewise, vitamin E may be protective against oxidative stress in lipotoxicity. Although these characteristics would make these agents appropriate for the treatment of NAFLD, their clinical use is thwarted by reports of toxicity on another organ system (increased rate of cardiac events for both PPAR-γ agonists and vitamin E).

Similar to lipotoxicity, deleterious metabolic changes may be caused by excess dietary intake of simple carbohydrates. Reports have shown that NAFLD patients with significant inflammation on liver biopsy report higher carbohydrate and simple sugar consumption than those without inflammation. In fact, high-carbohydrate diets are used in rodent models to generate NAFLD. Although the term glucotoxicity has been used to describe this phenomenon (implying a generalized effect from all carbohydrates), the most plausible culprit is the specific carbohydrate, high-fructose corn syrup. The obesity epidemic (with associated NAFLD) in the United States that has occurred over the past 4 decades parallels the increased consumption of high-fructose corn syrup (used as a sweetener, replacing pure cane sugar). Different dietary simple sugars may promote different patterns of fat distribution in obesity. In a mouse model, fructose promoted the development of hepatic fatty infiltration, whereas glucose promoted peripheral adiposity with relative sparing of the liver.

The concepts of lipotoxicity and glucotoxicity have important implications in the generation of “good fat vs bad fat.” Available data suggest that in the optimal situation, excess dietary calories would be stored as PUFA esterified into triglycerides in subcutaneous adipose tissue (“good fat”). In the worst-case scenario, excess calories would be deposited in the form of saturated free LCFA in more vital, nonadipose organs such as the heart and liver (“bad fat”).

Adipokines

The most important mechanism of inflammation in lipotoxicity associated with obesity is adipokine dysregulation (Figure 1). This topic deserves special attention because restoration of these pathways is central to immunonutrition in obesity. Adipokines are a group of soluble molecules that are largely secreted by white adipose tissue (WAT). A wide array of metabolically active molecules is produced by adipocytes and a group of cells associated with WAT known as stroma vascular fraction (SVF) cells (Table 1; ie, preadipocytes, fibroblasts, endothelial cells, histiocytes, and macrophages). This “cocktail” of inflammatory factors includes a complex mixture of cytokines, factors of the Complement cascade, and chemoattractant molecules (Table 1). In addition, increased levels of acute-phase proteins such as haptoglobin, C-reactive protein (CRP), interleukin IL-6, and serum amyloid A protein have been shown to correlate with increasing degrees of obesity. The increased expression or release of these mediators seen in obesity is ameliorated by weight loss.

Tumor Necrosis Factor-α (TNF-α). TNF-α is a critical proinflammatory cytokine associated with both the inflammation and insulin resistance seen in obesity. Release of TNF-α is tightly linked to increased circulating levels of FFAs, which, in turn, have been associated with increasing obesity, insulin resistance, and lipotoxicity. TNF-α is both a cause and an effect of increased circulating FFAs in obesity. Infusion of TNF-α has been shown to increase the amount of FFAs in circulation and worsen insulin resistance. Levels of TNF-α in
adipose tissue are positively correlated with the degree of obesity, as are levels of circulating FFAs.\textsuperscript{25,44,45} Shi et al\textsuperscript{25} demonstrated that certain FFAs induce production of TNF-\(\alpha\) from cultured macrophages via Toll-like receptor 4 (TLR4) and NF\(\kappa\)B activation. Particularly robust production of TNF-\(\alpha\) can be induced by the long-chain saturated fatty acids myristic, palmitic, and stearic acid. This inflammatory effect induced by FFAs is similar to that effect observed for endotoxin or lipopolysaccharide (LPS) although to a lesser extent, which also acts through binding of TLR4 and subsequent activation of NF\(\kappa\)B. These saturated FFAs are structurally similar to the lipid-A moiety of LPS, and it is probably this similarity that allows them to bind and activate TLR4. These data may indicate that the immune system cannot fully differentiate certain circulating FFAs from endotoxin or LPS. Therefore, to the immune system, obesity may be indistinguishable from chronic, low-grade, gram-negative, bacterial sepsis. The key effector of this interaction appears to be TNF-\(\alpha\), although other proinflammatory cytokines under NF\(\kappa\)B regulation are likely involved as well. The increased TNF-\(\alpha\) expression caused by FFAs can be almost completely blocked by docosahexaenoic acid (DHA), which is a component of both fish oil and many pharmaconutrition formulas.\textsuperscript{25} This information implies that fish oil may be an effective anti-TNF-\(\alpha\) agent in obesity.

Adiponectin. Adiponectin is a key mediator of obesity-associated insulin resistance and tissue inflammation. Considered a peripheral long-acting adipokine released from adipose tissue, adiponectin acts primarily by reducing inflammation and improving insulin sensitivity. Adiponectin exists in multiple isoforms with varying functions.\textsuperscript{37} Two receptors have been identified: adiponectin cellular receptor 1 (ADIPOR1) expressed widely throughout WAT and ADIPOR2 expressed mainly in the liver.\textsuperscript{37,39,46} In contrast to other adipokines, adiponectin is markedly reduced in individuals with visceral adiposity when compared with their lean counterparts.\textsuperscript{47} A number of factors have been shown to regulate the production of adiponectin by WAT, including TNF-\(\alpha\), IL-6, and PPAR-\(\gamma\).\textsuperscript{48–50}

Adiponectin exerts its anti-inflammatory effect through opposition to TNF-\(\alpha\).\textsuperscript{51} Adiponectin attenuates the macrophage response to TLR4 through the activation of ADIPOR1.\textsuperscript{52} In this way, adiponectin suppresses TLR4-induced NF\(\kappa\)B activation and suppresses the production of interferon-\(\gamma\) generated by LPS.\textsuperscript{53} By inhibiting the expression of adhesion molecules induced by TNF-\(\alpha\), adiponectin attenuates macrophage adherence, phagocytic capacity, and transmigration.\textsuperscript{54} In addition, adiponectin induces the production of other anti-inflammatory mediators (such as IL-10 and IL-1 receptor antagonist) by macrophages, monocytes, and dendritic cells. These molecular effects of adiponectin are illustrated in Figure 2 and Table 2.

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**Table 1.** Metabolically active molecules produced by adipocytes and stroma vascular fraction (SVF) cells of white adipose tissue (WAT)

<table>
<thead>
<tr>
<th>Cytokines</th>
<th>Tumor necrosis factor-(\alpha) (TNF-(\alpha))</th>
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<tr>
<td>Adiponectin</td>
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<td>Leptin</td>
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<td>Resistin</td>
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<td>Transforming growth factor-(\beta) (TGF-(\beta))</td>
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<tr>
<td>Interferon-(\gamma) (IFN-(\gamma))</td>
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<tr>
<td>Interleukins (IL-1, IL-6, IL-8, IL-10)</td>
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<td>Factors of the Complement cascade</td>
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<tr>
<td>Plasminogen activation inhibitor-1 (PAI-1)</td>
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<tr>
<td>Fibrinogen</td>
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<tr>
<td>Angiopoietin-related proteins</td>
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<tr>
<td>Complement factor-3</td>
<td></td>
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<tr>
<td>Chemoattractant molecules</td>
<td></td>
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<tr>
<td>Monocyte chemotactic protein-1 (MCP-1)</td>
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<tr>
<td>Macrophage inflammatory protein-1(\alpha) (MIP-1(\alpha))</td>
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**Figure 1.** Obesity-associated inflammation acts clinically as a chronic, low-grade SIRS response. This figure depicts the pathophysiological progression and underlying mechanisms that lead to insulin resistance, endothelial cell dysfunction (vasoconstriction), and release of cytokines. With the underlying systemic inflammation, obese patients exposed to secondary illness or injury may experience exaggerated infection, duration of mechanical ventilation, and mortality.

DM, diabetes mellitus; NAFLD, nonalcoholic fatty liver disease; OSA, obstructive sleep apnea; SIRS, systemic inflammatory response syndrome; TNF\(\alpha\), tumor-necrosis factor-\(\alpha\).
Finally, reduced circulating levels of adiponectin are a key component of obesity-induced insulin resistance and dyslipidemia. Treatment of obese animals with adiponectin has been shown to attenuate serum hyperglycemia, reduce levels of FFAs, and improve insulin sensitivity. Adiponectin directly stimulates β-oxidation of fat in hepatocytes and down-regulates the major transcription factor involved with lipid synthesis (sterol-regulatory-element-binding protein 1C). The role of adiponectin in improving insulin sensitivity appears to be mediated through phosphorylation of adenosine 5’ monophosphate-activated protein kinase (AMPK) and its subsequent activation in the liver. Through this same mechanism (AMPK activation), adiponectin has been shown to protect the myocardium from ischemia-induced apoptosis.

**Leptin.** Leptin, an adipokine produced and secreted by subcutaneous WAT, modulates food intake and energy balance by controlling appetite. Leptin regulates neuroendocrine function, energy homeostasis, hematopoiesis, and angiogenesis. Structurally, leptin is similar to other pro-inflammatory cytokines such as IL-6 and IL-12. Serum levels of leptin are proportional to overall adipose mass. High serum leptin and, more importantly, leptin resistance (implied by the failure of leptin to induce satiety) is observed in diet-induced obese rats.

In addition to controlling appetite, leptin also plays a role in both innate and adaptive inflammatory responses. Leptin has been shown to increase the production of pro-inflammatory cytokines from macrophages (TNF-α, IL-6, and IL-12) and hepatic stellate cells (MCP-1). The inflammatory response to leptin is, in part, mediated by the activation of NFκB and the subsequent production of TNF-α (an effect which is attenuated by release of adiponectin). Leptin causes proliferation of macrophages and leads to the activation, chemotraction, and cytotoxicity of both neutrophils and natural killer cells. These processes result in production of reactive oxygen species, raising the overall level of oxidative stress. These effects of leptin are illustrated in Figure 3A and Table 2.

**Resistin.** Resistin is a polypeptide adipokine produced by numerous tissues, including adipocytes, muscle, pancreatic tissues, and mononuclear cells. Expression of this adipokine is increased in response to IL-6, IL-1, TNF-α, and LPS. Adiponectin and PPAR-γ agonists have the opposite effect, decreasing synthesis and release of resistin. Expression of this adipokine is increased in response to IL-6, IL-1, TNF-α, and LPS. Adiponectin and PPAR-γ agonists have the opposite effect, decreasing synthesis and release of resistin. Increased resistin levels are associated with NFκB activation and the subsequent expression of numerous proinflammatory cytokines, including TNF-α, IL-1β, IL-6, and IL-12. Resistin has been implicated in the pathogenesis of type 2 diabetes mellitus, as studies have suggested a relation between increasing resistin levels and insulin receptor insensitivity. Finally, the effect of resistin on the microvasculature opposes that of adiponectin, such that resistin induces endothelial adhesion molecules, promoting injury to the vascular endothelium and increasing risk for atherosclerosis. These effects of resistin are illustrated in Figure 3B and Table 2.
Emerging Adipokines

Several new adipokines are now under investigation. Much like adiponectin, visceral adipose tissue-derived serine protease inhibitor (VASPIN) suppresses the production of leptin, TNF-α, and resistin and thus helps improve insulin sensitivity. Serum retinol-binding protein 4 (RBP4), released from adipose tissue, which lacks a specific glucose transporter, has the opposite effect, inducing insulin resistance and increasing risk for clinical diabetes mellitus. Finally, visfatin is a recently identified adipokine that decreases insulin resistance but has been linked in the past to several inflammatory disease states, such as acute lung injury (Table 2).

Pharmaconutrition

Delivery of enteral nutrition in the ICU has been shown to improve patient outcome. When used in the appropriate trauma, burn, or critically ill patient, formulas containing specific immune-modulating agents have been shown to have an increased benefit to that seen from standard formulas alone. In 2001, Heyland et al reviewed 22 randomized trials comparing pharmaconutrition (or previously termed immunonutrition) formulas to standard enteral diets. Use of the pharmaconutrition formulas decreased rates of infection, hospital LOS, and duration of mechanical ventilation compared with use of standard formulas. The benefits of pharmaconutrition involve down-regulation of the proinflammatory response in patients who already have exaggerated inflammation due to trauma, sepsis, or other critical illnesses. Because obesity induces a chronic, low-grade proinflammatory state, use of pharmaconutrition agents in obese patients may help down-regulate obesity-induced inflammation and improve metabolism. While there are many immunonutrients that might be potentially useful in obesity, Table 3 lists 11 of these.

ω-3 PUFAs

The fat composition of an ingested diet, in turn, determines the fatty acid composition of membrane phospholipids in cells such as white blood cells, endothelial cells, and tissue target cells. These fatty acids are broken down by specific phospholipases to produce prostaglandins, leukotrienes, thromboxanes, and other lipid-derived mediators during stress, such as trauma or infection. Diets rich in ω-3 PUFAs alter the prostaglandin and leukotriene profiles that are created during stress in a manner that reduces the host inflammatory response. Likewise, ω-3 PUFAs, specifically the eicosapentaenoic acid (EPA) and DHA components, reduce the inflammatory response through numerous distinct mechanisms. Studies have shown that ω-3 PUFAs down-regulate LPS-induced NFκB, which, in turn, decreases activation and release of TNF-α. In a specific animal model (db/db diabetic obese mice), ω-3 PUFAs were shown to inhibit infiltration of macrophages into WAT, thereby reducing the degree of inflammation subsequently induced within that tissue. Not surprisingly, diets rich in ω-3 PUFAs have been shown to improve inflammatory symptoms in other disease processes such as arthritis and ulcerative colitis.

In addition to their impact on systemic inflammation, ω-3 PUFAs have a favorable effect on metabolism. PUFAs nonspecifically activate PPAR-γ and PPAR-α, 2 agents that have been shown in an animal model to increase both basal and postprandial glucose-induced insulin production from pancreatic islet cells. ω-3 PUFAs have been shown to

<table>
<thead>
<tr>
<th>Adipokines</th>
<th>Overall action</th>
<th>Role within the innate immunity</th>
<th>Associated diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adiponectin</td>
<td>Anti-inflammatory</td>
<td>↑ IL-10, IL-1RA</td>
<td>DM, OSA, NAFLD, ASH, CAD, RA, cancer, IBS</td>
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<tr>
<td></td>
<td></td>
<td>↓ NFκB-mediated endothelial adhesion molecule expression and cytokine release, phagocytosis, IL-6, TNF-α, and IL-1β</td>
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<tr>
<td>Resistin</td>
<td>Proinflammatory</td>
<td>↑ VCAM1, ICAM1, IL-6, TNF-α, IL-1β</td>
<td>DM, OSA, NAFLD, CKD, CAD, RA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>↓ NFκB-mediated endothelial adhesion molecule expression and cytokine release</td>
<td></td>
</tr>
<tr>
<td>Leptin</td>
<td>Proinflammatory</td>
<td>↑ TNF-α, IL-6, IL-12, neutrophil activation, ROS release and chemotaxis, NK-cell function, macrophage activation, and cytokine release</td>
<td>OSA, NAFLD, asthma, cancer</td>
</tr>
<tr>
<td>Visfatin</td>
<td>Proinflammatory</td>
<td>↑ IL-6, IL-8; ↓ apoptosis of neutrophils</td>
<td>Sepsis, acute lung injury, DM</td>
</tr>
</tbody>
</table>

ASH, alcoholic steatohepatitis; CAD, coronary artery disease; CKD, chronic kidney disease; DM, diabetes mellitus; IBS, irritable bowel syndrome; ICAM, intercellular adhesion molecule; IFN-γ, interferon-γ; IL, interleukin; IL-1RA, IL-1 receptor antagonist; NAFLD, nonalcoholic liver disease; NFκB, nuclear factorκB; NK, natural killer; OSA, obstructive sleep apnea; RA, rheumatoid arthritis; ROS, reactive oxygen species; TNF-α, tumor-necrosis factor-α; VCAM, vascular cell-adhesion molecule.
decrease serum triglyceride levels and may favorably alter adiponectin levels.\textsuperscript{79} As a result of the decreased inflammation, reduced triglycerides, and increased adiponectin, it is not surprising that \( \omega-3 \) PUFAs have been shown to ameliorate the pathophysiology of NAFLD. In a prospective randomized trial, patients with NAFLD who received 1 g/d of \( \omega-3 \) PUFA for 12 months had significantly decreased serum levels of alanine aminotransferase, aspartate aminotransferase, \( \gamma \)-glutamyl transferase, and triglycerides compared with controls who took a placebo.\textsuperscript{80} Circulating arachidonic levels and the serum ratio of \( \omega-6/\omega-3 \) fatty acids were reduced in study patients compared with con-

\begin{figure}[h]
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\caption{A, Leptin signals increase proinflammatory cytokines (TNF, IL-6, and IL-12), induce nitric oxide synthase-2 (NOS-2 or inducible NOS), increase reactive oxygen species (ROS), and activate monocytes. B, Resistin signals increase proinflammatory cytokine production (TNF, IL-1, IL-6, and IL-12), but its role in monocyte activation is unclear. Whereas adiponectin can be considered an anti-inflammatory strategy of the “adipose organ,” leptin and resistin have dominant proinflammatory features. I\( \kappa \)B, inhibitor of NF\( \kappa \)B; LPS, lipopolysaccharide; PPAR, peroxisome-proliferator-activated receptor; TLR4, Toll-like receptor 4. Figure reprinted and legend adapted by permission from Macmillan Publishers Ltd: [Nature Reviews Immunology],\textsuperscript{51} Copyright © 2006.}
\end{figure}
controls. Liver ultrasonography performed after treatment showed significant improvement in hepatic echo-texture and increased Doppler perfusion, suggesting improvement in liver blood flow in response to ω-3 PUFA supplementation. NAFLD has been associated with decreased liver perfusion, which may place patients at increased risk during trauma or critical illness. In an animal model, diets supplemented with ω-3 PUFAs, RNA fragments, and arginine were found to increase distal small intestinal blood flow when compared with isocaloric, isonitrogenous control diets (without the immune-modulating agents). Soy protein may also promote adipocytes of leptin-resistant rats, soy protein may place patients at increased risk during trauma or critical illness. In an animal model, diets supplemented with ω-3 PUFAs, RNA fragments, and arginine were found to increase distal small intestinal blood flow when compared with isocaloric, isonitrogenous control diets (without the immune-modulating agents).

The appropriate dosage of ω-3 PUFA supplementation to treat the metabolic syndrome has not been determined. A valuable reference point for clinicians might be the Food and Drug Administration (FDA)-approved doses recommended for treatment of hypertriglyceridemia, which are 1860 mg/d of EPA and 1500 mg/d of DHA.

**Soy Protein**

Soy provides a high-quality vegetable protein source that may help reduce risk of lipotoxicity and the metabolic syndrome. In rat pancreatic islet cells, soy protein has been shown to decrease high-fat diet-induced hyperinsulinemia and raise glucose levels (when compared with casein diets). In adipocytes of leptin-resistant rats, soy protein may increase PPAR-γ expression, resulting in adipocyte hyperplasia (but not hypertrophy). In various animal models, soy protein has been shown to be associated with increased serum adiponectin, decreased plasminogen activator inhibitor, and improved fatty liver (via decreased expression of the lipogenic transcription factor sterol regulatory element-binding protein [SREBP]-1, and increased lipid oxidation due to activation of PPAR-α). Soy protein may also promote cholesterol uptake by the liver, thus lowering serum cholesterol. The beneficial effects of soy protein in obesity and NAFLD are illustrated in Figure 4.

Although clinical studies in obese humans are limited, available data suggest that soy protein may have a role in the treatment of obesity and dyslipidemia. In an outpatient weight loss study, daily provision of 90 g of soy protein in meal replacement shakes resulted in a 2.5-fold greater weight loss than a control diet. Isoflavones (available in most but not all soy preparations) have estrogenic activities and seem to mediate many of the beneficial effects of soy seen in obesity. Because of their estrogenic effect, these compounds may be contraindicated in certain conditions such as breast cancer. Although rare in adults, soy protein allergy occurs in 3%–4% of infants and children, an incidence that compares favorably to the allergy profile of cow’s milk (25% in infants and children).

**i-Leucine**

Sarcopenia is a syndrome of muscle wasting normally seen as a consequence of a prolonged medical illness such as cancer or COPD. By inducing inflammation, obesity may play an important role in the development of age-related sarcopenia. Thus, decreasing total body mass while maintaining or increasing skeletal muscle lean body mass is an important consideration when treating obesity, and the metabolic syndrome and may be achieved by providing a high-protein, low-carbohydrate regimen. Dietary amino acids are known to stimulate protein synthesis, but this is not simply due to the provision of increased exogenous substrate. Rather, the anabolic effects of dietary protein seem to be mediated almost entirely by the molecular signaling of the single amino acid, leucine. Leucine activates the initiation phase of protein translation at several levels. Clinical studies indicate that an intake of as little as 2.5 g of leucine acutely stimulates muscle protein synthesis. When given chronically with meals as part of a protein-rich weight-loss diet, leucine causes proportionally greater loss of body fat, with relative sparing of lean body tissue. Through a hypothalamic “fuel sensor” mechanism that regulates hunger and satiety, leucine may provide additional benefit as an anorexigenic agent in the treatment of obesity.

The combination of leucine and soy protein may be a particularly potent anabolic combination. Although not studied in obesity, soy protein supplemented with leucine enhanced whole-body protein synthesis in patients with COPD. When used pharmacologically, it is important to obtain adequate “drug levels” of leucine. It seems that peak levels are critical, and leucine should be given in boluses of at least 2.5 g, which can be repeated several times daily to obtain a total daily dose of 6–8 g.

**i-Arginine**

Arginine is a nonessential amino acid under normal physiologic conditions, which becomes essential under conditions of increased stress, including sep-
Arginine is metabolized through variable pathways, including inducible nitric oxide synthase (NOS) and arginase I and II, all of which are up-regulated during inflammation. Arginine is involved in regulation of vascular tone, modulation of white blood cell function, and control of wound healing. Dietary arginine supplementation promotes wound healing by enhancing protein synthesis of proline and hydroxyproline (via ornithine).

Arginine acts as a secretagogue by stimulating release of insulin and insulin-like growth factor (IGF-1). Depressed T-cell-mediated immunity, seen commonly after major surgery or trauma, can be ameliorated by arginine supplementation.

Asymmetric dimethylarginine (ADMA) is a metabolic byproduct of cytoplasmic protein processing. Because it is structurally similar to L-arginine, ADMA appears to interfere with NOS function. ADMA is elevated in the blood of patients with cardiovascular risk factors such as hyperlipidemia, hypertension, obstructive sleep apnea, diabetes, homocysteinemia, and obesity. Elevated ADMA concentrations in obese, insulin-resistant women can be modulated by weight loss. These elevated levels of ADMA associated with obesity might explain the endothelial dysfunction seen in the metabolic syndrome. The imbalance of ADMA and arginine often seen with obesity is illustrated in Figure 5.

In patients with elevated ADMA, L-arginine supplementation may provide beneficial effects by competing with circulating ADMA levels for normal regulatory processes. Patients with normal ADMA levels seem to be unaffected by arginine supplementation. In a rat model of NAFLD, L-arginine supplementation enhanced the hepatic microcirculation and directly increased blood flow through the hepatic artery and portal vein. These effects on hepatic blood flow were reversed when nitric oxide was blocked by giving L-NAME, an agent that is similar in structure to ADMA. These data suggest that L-arginine supplementation may increase hepatic perfusion and thus could possibly reverse the hepatic endothelial dysfunction that occurs in NAFLD.

Arginine is extensively metabolized, and there have been recent concerns that this phenomenon may hamper its usefulness, especially at lower doses. Commercial enteral formulas supplemented with arginine provide approximately 12.5 g of arginine per 1000 kcal, which should deliver a reasonable dose for most patients. An alternative strategy is the administration of the amino acid, citrulline, which is a prodrug that is converted into arginine. A recent study in human volunteers showed that orally administered citrulline improved the arginine to ADMA ratio in a dose-dependent fashion, with the greatest effects occurring at 3 g twice daily.
arginine increases nitric oxide levels, it is theoretically contraindicated in patients with systemic septic shock and hypotension.

Betaine and S-Adenosylmethionine

Trans-methylation and trans-sulfuration pathways are affected by obesity and NAFLD (Figure 6). Homocysteine, a sulfur-containing intermediate, may become elevated with insulin resistance and the metabolic syndrome. Hyperhomocysteinemia has been associated with a variety of adverse effects, including endothelial dysfunction, decreased ADMA catabolism, impaired methylation, and oxidative stress. These changes lead to an increased risk of cardiovascular disease and possibly nonalcoholic steatohepatitis (NASH).

Betaine (trimethylglycine), originally discovered in the juice of sugar beets, serves as a methyl donor and functions to protect cells from osmotic stress. Betaine reduces circulating levels of homocysteine by facilitating its conversion back to methionine, which also decreases S-adenosyl homocysteine (SAH). In a rat model, decreased betaine levels were observed in the setting of fatty liver. Betaine has been successfully used in a pilot study in NASH patients.

S-adenosylmethionine (SAMe) is the major methyl group donor in humans but has several other actions independent of methyl donation, which may also be important. SAMe is formed from methionine and ATP in a reaction catalyzed by methionine adenosyl transferase (MAT; Figure 6). After methyl donation, SAMe is converted to SAH (Figure 6). Oxidative stress in NAFLD may lead to hepatic SAMe depletion through a variety of mechanisms, including decreased MAT activity. A vicious cycle may ensue because SAMe deficiency can promote oxidative stress through reduced glutathione production. In a MAT knockout mouse model, SAMe deficiency may promote steatohepatitis. An increased SAH:SAMe ratio, which is a hallmark of many forms of liver disease such as NAFLD, may also occur in diabetes and diabetic nephropathy. SAH, which may be converted to homocysteine, is a toxic metabolite that sensitizes the liver to TNF-α induced hepatotoxicity. In a multicenter clinical trial, SAMe improved clinical outcome in alcoholic liver disease, a disease process that is very...
similar to NAFLD. In LPS-stimulated monocytes, SAMe has also been shown to down-regulate the proinflammatory cytokine TNF-\(\alpha\) while up-regulating the anti-inflammatory cytokine interleukin 10. According to these results, SAMe would be an appropriate agent to treat NAFLD. SAMe is also an emerging treatment for depression and osteoarthritis, both of which are associated with obesity and the metabolic syndrome.

Insufficient clinical data exist to make firm dosage recommendations for betaine and SAMe in obesity and the metabolic syndrome. However, the dosages likely reflect those used for liver disease. In these studies, betaine was given at a dose of 10 g twice daily, and SAMe was given at a dose of 1.2 g, typically in 3 divided doses of 400 mg each.

\(\epsilon\)-Carnitine

In humans, 75% of carnitine comes from dietary sources, the remainder being synthesized in the liver, kidney, and brain after methylation of lysine. Some evidence suggests that carnitine biosynthesis is impaired in the setting of SAMe deficiency. The overwhelming majority (99%) of carnitine is intracellular. Carnitine is concentrated in skeletal and cardiac muscle, where it supports mitochondrial \(\beta\)-oxidation of fatty acids (Figure 7). Carnitine influences carbohydrate metabolism by modulating the ratio acyl-CoA:CoA (Figure 7).

Carnitine insufficiency is likely when the serum ratio of conjugated to free carnitine is \(>0.4\). In an animal model of carnitine deficiency (the juvenile visceral steatosis mouse), lipotoxic cardiomyopathy and NAFLD readily occur with hepatic accumulation of the long-chain saturated fatty acids palmitate and stearate. Likewise, carnitine deficiency has been implicated in fatty liver associated with parenteral nutrition (PN). Carnitine deficiency has been associated with many other medical diseases, including cirrhosis, chronic kidney disease, valproic acid therapy, Alzheimer’s disease, and heart failure. Muscle carnitine levels have been shown to decline with aging. Patients with type 2 diabetes (particularly those who are insulin dependent or have complications of their disease process) seem to be at increased risk for carnitine deficiency.

Evidence is mounting that carnitine supplementation may be beneficial in obesity, insulin resistance, and the metabolic syndrome. Older studies indicated that neither oral nor IV carnitine supplementation altered carnitine levels in skeletal mus-
However, it now seems that carnitine transport into skeletal muscle after oral feeding does occur in the setting of hyperinsulinemia, high-carbohydrate diet, or insulin infusion. In animal models, at least, such is the case. In spontaneously hypertensive rats, carnitine has been shown to attenuate lipid peroxidation and increase antioxidant defenses. In obese rats with insulin resistance, carnitine supplementation improved glucose tolerance and increased total energy expenditure. Carnitine supplementation data from human clinical studies are limited. However, carnitine has been shown to attenuate endothelial dysfunction caused by elevation of FFAs. Furthermore, acetyl-carnitine has been shown to be an effective treatment for diabetic neuropathy at doses ranging from 1.5 to 3 g/d.

In documented cases of carnitine deficiency, the FDA has approved an oral replacement dose ranging from 1.98 to 2.97 g/d. The optimal dose for supplementation in obesity and the metabolic syndrome is unknown, but a range of 1.5–3.0 g/d is reasonable until more data become available. Carnitine may have several gastrointestinal side effects, including abdominal pain, vomiting, and diarrhea. Caution is advised if there is an underlying seizure disorder.

**Magnesium**

After potassium, magnesium is the most abundant intracellular cation, having numerous roles in health and disease. Magnesium is a cofactor for more than 300 enzymes involved in bioenergetics, protein phosphorylation, glutathione production, and synthesis of cyclic adenosine monophosphate (cAMP). Magnesium availability affects the structure and function of nucleic acids, cell membranes, and ion channels.

Because the magnesium content of food is greatly reduced by processing, it is estimated that 75% of...
Americans do not meet the recommended daily allowance (420 mg for men, 320 mg for women). Magnesium is stored intracellularly, and as such, serum magnesium concentration does not necessarily reflect whole body magnesium stores (serum levels can be normal in clinically deficient states).

Strong epidemiologic and mechanistic data support a role for magnesium deficiency in the genesis of insulin resistance and the metabolic syndrome. Magnesium deficiency contributes to the development of the metabolic syndrome (and, conversely, may also be caused by the metabolic syndrome). Multiple studies have associated magnesium deficiency with obesity, diabetes, diabetic vascular complications, dyslipidemia, hypertension, NASH, insulin resistance, and the metabolic syndrome. The mechanism of this effect in obese humans is multifactorial and involves reduced tyrosine kinase activity at the insulin receptor, modulation of intracellular calcium activity, and increased circulating TNF-α levels (Figure 8).

Magnesium deficiency is most commonly precipitated by the combination of suboptimal dietary consumption and increased renal losses. Large, long-term, population-based studies have shown that increased dietary magnesium consumption is protective against the development of diabetes and the metabolic syndrome. The insulin-sensitizing drugs metformin and pioglitazone may exert their clinical effects, in part, by favorably modulating magnesium levels.

Small clinical studies have shown that oral magnesium replacement (2.5 g magnesium chloride for 16 weeks) increases insulin sensitivity in diabetic and nondiabetic patients with magnesium deficiency. Magnesium replacement therapy may be reasonable for individuals who already have or are at risk for the subsequent development of the metabolic syndrome. In the absence of renal insufficiency, dietary intake should exceed the recommended daily allowance to overcome potential renal losses. The absolute dose will likely vary, according to a patient’s individual degree of deficiency and renal function. As magnesium is replaced orally, patients should be monitored for the development of diarrhea.

Zinc

Zinc is the second most abundant trace metal in the human body. Zinc is a cofactor in over 300 metalloenzymes involved in gene transcription, metabolism, membrane stability, and inflammation. Although tissue zinc status is the critical determinant of zinc deficiency, serum zinc levels may be used clinically as a surrogate marker for overall body stores. Decreased serum zinc concentrations have been observed in obesity, insulin resistance, diabetes, and hypertension. Similar to magnesium, zinc deficiency is most commonly precipitated by inadequate dietary intake and increased renal losses. Estimates suggest that only 56% of Americans have adequate zinc intake according to the recommended daily allowance (15 mg for adult men; 12 mg for nonlactating women).

The effect of obesity on tissue zinc levels is complicated; therefore, stores may not be reflected accurately by serum levels. In obesity, the expression of multiple zinc transporter proteins in the adipose tissue itself is altered, an effect that may differ appreciably from one region to another (eg, subcutaneous to intra-abdominal adipose tissue).

Zinc status modulates obesity and the metabolic syndrome. In a large clinical study, both low consumption of dietary zinc and low serum zinc levels were associated with an increased prevalence of diabetes, hypertension, hypercholesterolemia, and coronary artery disease. In a recent study of fatty liver disease, patients with steatohepatitis consumed less zinc that those with simple steatosis (a much milder form of the liver disease).

Animal studies have demonstrated potential mechanisms and implied a plausible therapeutic role for zinc in obesity. In mice, a high-fat diet was associated with reduced zinc concentrations in adipose tissue, which, in turn, negatively correlated with serum leptin levels. In rats fed a high-fructose diet, zinc supplementation improved insulin sensitivity and antioxidant status. Zinc is a potent antioxidant and provides a protective effect against ischemia/reperfusion injury, which could be relevant for critically ill obese patients. Acutely, zinc administration stabilizes sulfhydryl groups and antagonizes redox-active transition metals to prevent the development of diabetes and the metabolic syndrome.

Figure 8. Intracellular magnesium deficiency might mediate the relationship between insulin resistance, hypertension, metabolic syndrome, and type 2 diabetes mellitus. Adapted from Archives of Biochemistry and Biophysics, Vol. 458; Barbagallo M, Dominguez LJ; Magnesium metabolism in type 2 diabetes mellitus, metabolic syndrome and insulin resistance; pp. 40–47; Copyright © 2007, with permission from Elsevier.
decrease free radical formation.\textsuperscript{161} Chronically, zinc administration induces metallothioneins, potent free radical scavengers, which have been shown in the past to prevent lipotoxic cardiomyopathy.\textsuperscript{161,162} Zinc deficiency causes cell-mediated immune dysfunction, proinflammatory cytokine dysregulation, and increased TNF-\(\alpha\) expression.\textsuperscript{163} Zinc supplementation, on the other hand, is protective against TNF-\(\alpha\)-mediated hepatotoxicity, protects small bowel structural integrity and barrier function, and ameliorates symptoms of diarrhea.\textsuperscript{164}

The fact that obesity has been associated with decreased serum zinc levels has important implications in the therapeutic management of inflammation, oxidative stress, and the genesis and progression of the metabolic syndrome. Although data are insufficient to make evidence-based dosing recommendations for zinc supplementation, a 220 mg daily dose of zinc sulfate is commonly used for wound healing applications, and might be a starting point for treatment in obesity. Common side effects are limited to nausea, which may be reduced by prescribing alternate forms of zinc (such as zinc acetate).

\textbf{\(\alpha\)-Lipoic Acid}

\(\alpha\)-Lipoic acid (ALA), a potent antioxidant synthesized by both plants and animals, is a cofactor for several mitochondrial enzyme complexes.\textsuperscript{165} When reduced to \(\alpha\)-dihydrolipoic acid (DHLA) by intracellular enzymes, the compound directly interacts with reactive oxygen and nitrogen species.\textsuperscript{165} DHLA restores the antioxidant activity of glutathione, vitamin C, and coenzyme Q\textsubscript{10} and has been shown to increase cellular uptake of cysteine (thereby enhancing glutathione synthesis).\textsuperscript{165}

ALA also has numerous immunomodulatory or anti-inflammatory effects. ALA has been shown to attenuate LPS-induced monocyte activation, reduce production and subsequent tissue damage by TNF-\(\alpha\), and protect against endotoxin-induced oxidative stress.\textsuperscript{166,167} ALA increases cyclic AMP in human T cells and natural killer cells, which serves to reduce inflammation.\textsuperscript{168}

ALA may have an emerging clinically relevant therapeutic role in metabolism. In rats, ALA binds and activates the insulin receptor\textsuperscript{169} and has been shown to restore insulin sensitivity during high-fructose feeding.\textsuperscript{170} In obese patients with type 2 diabetes, 600 mg of ALA by mouth twice daily nearly doubled peripheral insulin sensitivity over a 4-week period.\textsuperscript{171} In an animal model of obesity, ALA reduced body weight and prevented triglyceride accumulation in skeletal muscle and pancreatic islets, an effect that helped prevent diabetes.\textsuperscript{172} In the same model, ALA was shown to prevent skeletal muscle lipotoxicity by increasing fatty acid oxidation.\textsuperscript{173} Diabetic neuropathy symptoms were improved in 26\% to 62\% of patients treated with oral ALA at doses ranging from 600 to 1800 mg daily over 5 weeks.\textsuperscript{174} Through modulation of AMP-activated protein kinase in the hypothalamus of rodents, ALA has been shown to promote anorexia and reduce food intake, enhance energy expenditure, and promote significant weight loss.\textsuperscript{175}

ALA may also help ameliorate long-term complications of cardiovascular disease. In patients with diabetes and end-stage renal disease requiring hemodialysis, ALA supplementation significantly reduced plasma levels of ADMA, mentioned earlier in this manuscript to be a marker of endothelial dysfunction and cardiovascular outcome in these patients.\textsuperscript{176} In obese rats, ALA mitigated endothelial dysfunction\textsuperscript{177} and diet-induced hypertension.\textsuperscript{170} In a genetic, murine model of cardiac lipotoxicity, ALA normalized cardiac triglyceride accumulation to restore myocardial function.\textsuperscript{178}

Human studies indicate that an oral dose of 600 mg daily provides the optimal risk:benefit ratio. Side effects of treatment are limited to a dose-dependent increase in nausea, vomiting, and vertigo.

\textbf{Potential Role of Pharmaconutrition in Obesity}

Interesting generalizations can be made from this body of information. It is clear that adipose tissue is not clinically “inert” but represents a true endocrine organ with active secretory capabilities. Obesity serves to up-regulate systemic inflammation, creating a low-grade systemic inflammatory response syndrome (SIRS) response. The location where fat is deposited in a situation of excess caloric provision relates to the subsequent morbidity. Subcutaneous fat (as seen in peripheral adiposity) appears to be tolerated best and may represent the optimal response to excess calories. Fat surrounding the viscera (seen in central adiposity) is more deleterious and more likely to be associated with the metabolic syndrome. But fat deposited within the viscera is the worst-case scenario, leading eventually to organ dysfunction at sites such as the liver, pancreas, heart, and skeletal muscle. In fact, excess lipid accumulation exceeding the innate storage capacity of these ectopic organs is what causes lipotoxicity and leads to cellular and ultimately organ dysfunction.

The SIRS associated with obesity drives the metabolic syndrome. The clinical picture of insulin resistance, central adiposity, and organ dysfunction is similar in cytokine profile, picture of inflammation, and morbidity to that seen with gram-negative sepsis, although less severe than that seen in sepsis. Dietary intake can further modulate the level of inflammation. Exogenous long-chain saturated fat, via the TLR-4 receptors, can further increase inflammation (and polyunsaturated or monounsaturated fat may decrease inflammation). In fact, the immune system appears to have difficulty distinguishing between saturated fat in the diet and bacterial endotoxin.
The existence of a preexisting state of inflammation as a result of obesity may fulfill the classic 1-hit–2-hit pattern of immune stimulation. The first hit is the obesity itself, which increases the production of NFκB and TNF, essentially “priming” the immune system. The second hit is the clinical insult itself: the bariatric surgery, trauma, burn, pneumonia, or myocardial infarction. The clinical manifestation of the 1-hit–2-hit phenomenon is that the priming of the immune system from the preexisting disorder (obesity) leads to an exaggerated immune response with the secondary injury (surgery, trauma, sepsis, etc). The significance of this condition at the bedside means that the critically ill, obese patient hospitalized for any reason will have greater risk for organ failure, hyperglycemia, insulin resistance, infectious morbidity, longer ICU LOS, prolonged duration of mechanical ventilation, and greater mortality compared with their lean counterparts.

The challenge, therefore, is developing a nutrition formula for obesity that is capable of altering the metabolic state, removing fat from the liver, improving organ function, down-regulating systemic inflammation, and attenuating the morbidity associated with this disease process. The downside to developing any obesity formula is the realization that providing more calories to a patient who is already in obvious excess energy balance may have a deleterious effect. Weight loss may not be required, however, to convert an obese, unhealthy patient to a similar-weight but healthier patient, as long as there is improvement in insulin sensitivity, organ dysfunction, and level of inflammation.

The design of a regimen for obesity overall should be low-calorie, high-protein, preferably 0.75 kcal/mL or less in caloric density. The macronutrient composition should include a mix of specific proteins, including arginine, leucine, and soy protein. The fat should be predominantly ω-3 PUFAs, preferably in the form of fish oil. To this overall mixture, specific additives (such as SAMe or betaine, carnitine, magnesium, zinc, and ALA) should be added in appropriate doses.

In the outpatient setting, it would be unrealistic to provide such a formula to the general obese population. The cost would be prohibitive and these patients might not be motivated to lose weight. In fact, these are the types of patients that would be less likely to “budget” their intake to accommodate the extra calories in an oral specialty-designed supplement. But a motivated, ambulatory, obese patient in an outpatient weight-loss program might benefit substantially from a specialty formula designed for obesity. The formula could be substituted for 1 or 2 meals a day, and thus would have to be palatable and good-tasting enough for oral consumption. The regimen should promote “safe” weight loss by optimizing fatty acid oxidation and preventing fatty accumulation in the liver as the patient loses weight. In the patient awaiting bariatric surgery, it might even be worth delaying the surgery to decrease the SIRS response, improve insulin sensitivity, and remove fat from the liver preoperatively.

In the critically ill patient, a pharmaconutrition formula for obese patients might provide even greater benefit with respect to patient outcome. Here, a formula would be designed for tube feeding. Current recommendations from the 2001 Summit on Immunonutrition clearly identified “candidates” for immune-modulating formulas according to the strength of the literature that indicated for which patient population use of immunonutrition would clearly change outcome.177 Certainly, prospective, randomized trials would have to be performed in obese patients before clear conclusions and a specific design could be made. However, the information culled from the current animal studies and limited clinical experience suggests that such a formula is a plausible therapeutic strategy and that “obesity” would be added to this list of indications for a pharmaconutrition formula in the future.

The limitations of this concept are considerable. It would be preferable to evaluate each component separately to determine the specific optimal dose. Findings in animal studies do not always correlate to clinical studies, or at least, the clinical studies may not see as dramatic an effect. Compatibility issues, solubility, and stability may preclude the simple addition of some of these agents. Interaction or synergism between agents with regard to their profile of side effects again may prevent the combination of certain individual nutrients. Any benefit gained from a pharmaconutrition formula could be offset by excess net caloric intake and subsequent weight gain. Finally, the enthusiasm generated from small early studies may be lost if results cannot be replicated when larger clinical studies are eventually conducted.

Conclusions

The current obesity epidemic presents unique problems in healthcare. Obese patients who sustain trauma or develop critical illness seem to be at increased risk and are more likely to experience adverse outcomes than their lean counterparts. Obesity is associated with organ dysfunction and chronic smoldering inflammation. These effects are mediated by lipotoxicity and adipokine dysregulation. New data indicate that obesity-induced inflammation may be mechanistically similar to chronic, low-grade, gram-negative sepsis. This inflammatory response may partially explain worse ICU outcomes in obese patients. The current state of the art for the nutrition therapy of obese patients is limited to high-protein, hypocaloric enteral or parenteral feeding. This approach probably does little to reverse obesity-associated inflammation. Key immunonutrients in categories ranging from specialized fat and protein derivatives to individual minerals and anti-
oxidants can potentially attenuate the inflammatory state and correct the metabolic derangements in obese patients even in the absence of weight loss. We advocate the implementation of this knowledge to develop rationally designed pharmaconutrition regimens that could lessen the morbidity and improve outcome for patients with obesity.

References


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