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Review Article

The Chronic Inflammatory Hypothesis for the Morbidity Associated with Morbid Obesity: Implications and Effects of Weight Loss

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Background: Obesity is a worldwide pandemic that causes a multitude of co-morbid conditions. However, there has been slow progress in understanding the basic pathophysiology that underlies co-morbid conditions associated with obesity. Recently, there has been intense interest in the role of inflammation in obesity. Using the inflammatory hypothesis, many of the mechanisms by which co-morbid conditions are associated with obesity are being elucidated.

Methods: We searched the literature and reviewed all relevant articles. We focused on hormones and cytokines that have been associated with other inflammatory conditions such as sepsis and systemic inflammatory response syndrome.

Findings: Angiotensinogen (AGT), transforming growth factor beta (TGF\textbeta{}), tumor necrosis factor alpha (TNF\textalpha{}), and interleukin six (IL-6) are all elevated in obesity and correlate with several markers of adipocyte mass. These mediators have detrimental effects on hypertension, diabetes, dyslipidemia, thromboembolic phenomena, infections, and cancer. Weight loss results in a reduction of inflammatory mediators and a diminution of the associated co-morbid conditions.

Conclusions: The success of weight loss surgery in treating the complications associated with obesity is most probably related to the reduction of inflammatory mediators. While some aspects of bariatric physiology remain unclear, there appears to be a strong association between obesity and inflammation, thereby rendering obesity a chronic inflammatory state. A clearer understanding of the physiology of obesity will allow physicians who treat the obese to develop better strategies to promote weight loss and improve the well-being of millions of individuals.

Key words: Obesity, morbid obesity, inflammation, angiotensin, hypertension, leptin, tumor necrosis factor, transforming growth factor, interleukin, insulin resistance, infection, cancer, C-reactive protein, serum amyloid A

Introduction

Obesity, defined as a BMI >30 kg/m\textsuperscript{2}, is a global epidemic that currently affects over 185 million adults in industrialized nations, 115 million in the developing world and over 18 million children under the age of five.\textsuperscript{1,2} Patients who have a BMI >25 are considered overweight, while a BMI >30 is considered obese, and a BMI >40 is considered morbidly obese. In the US, >27% of the population is currently obese, with over half of the population being overweight. There are approximately 260,000 to 380,000 deaths a year from factors related to obesity in the US.\textsuperscript{3} This exceeds the aggregate totals of lung (154,000), colon (48,000), breast (40,000) and prostate (30,200) cancer combined.\textsuperscript{4} The BMI has

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served as a useful clinical tool in the evaluation of obesity and the appropriateness of patients for surgery. However, as a measure of total fatness, the BMI measurement fails because it underestimates the total amount of fat in females (females have more fat mass than men at similar BMIs) and overestimates fat mass in muscular men. A potentially useful addition to the appraisal of health risks of obesity would be biologic markers that assess the amount of excess inflammation.

Recently there has been rising interest in the role of inflammation in the morbidity obese. C-reactive protein (CRP), an acute phase reactant, has undergone intense investigation. Its elevation corresponds to the level of adiposity present in the body. Additionally, this protein functions as a valuable tool to predict future cardiovascular events such as ischemic stroke, coronary heart disease, myocardial infarction, peripheral arterial disease, and mortality in men and women. Yet, this protein plays only a small role in the acute phase response. The acute phase response was associated with at least 45 different proteins and an extended list of associated phenomena. We can draw meaningful conclusions from the data already present in the literature. Using a model of an increased adipocyte mass functioning as an endocrine organ, we can gain further insights into the dyslipidemic, oncologic, infectious, diabetic, hypertensive, and thromboembolic phenomena that plague morbidly obese patients. Additionally, we may gain insight as to why weight loss surgery is successful in reversing the complex metabolic phenomena associated with obesity.

**Adipose Tissue as an Endocrine Organ**

Until recently, it was accepted that the role of the adipocyte was the passive storage of energy in the form of white fat, or of brown fat for thermogenesis. The function of these cells was thought to be the release of fatty acids in times of starvation or the production of heat in times of cold, respectively. However, with the explosion of obesity-related research, it has become clear that fat cells actively monitor their environment, and vigorously respond to neural, paracrine, autocrine and endocrine inputs. These inputs include a wide array of steroids, cytokines, prostaglandins, cholesterol, and fatty acids (Table 1). It has also become clear that the adipocyte produces numerous secretions. While it is beyond the scope of this paper to investigate all secretions of the adipocyte, we can review those that are implicated in initiating the chronic inflammatory response that is associated with obesity (Table 2).

The most notable inflammatory mediators released by the adipocyte are angiotensinogen (AGT), transforming growth factor beta (TGFβ), tumor necrosis factor alpha (TNFα), and interleukin six (IL-6).

**Angiotensinogen**

AGT is a 60 Kd protein originally thought to be produced in significant amounts only in the liver. This protein, which does not possess any independent biological activity, is the first step in the renin angiotensin system. Renin cleaves AGT to produce angiotensin I which has little biologic activity. Next, Angiotensin I is cleaved by angiotensin-converting enzyme (ACE) in the lung, to produce angiotensin II. Angiotensin II creates a system of biologic actions as will be described later. The main feature of this system is the regulation of blood pressure in the face of dehydration or hypovolemic shock. One of the early responses to declining renal perfusion is the hepatic production of AGT. The production of AGT in response to inflammation and shock has led to its recognition as an acute phase protein. However, when the renin-angiotensin system becomes dysfunctional, as in renovascular occlusive disease, it manifests itself as hypertension.

Recently, a significant elevation of angiotensinogen levels has been shown to correlate directly with leptin levels (a marker of adipocyte mass) and BMI. These high levels are not caused by an overproduction of AGT from the liver, as indicated by the positive correlation between BMI and subcutaneous adipocyte angiotensinogen mRNA expression. However, the overproduction of angiotensin is not, by itself, important, since it and its metabolite angiotensin I are both inactive proteins. These proteins are acted on by renin and angiotensin converting enzyme, which have both been shown, using
Table 1. Known endocrine hormones and secretions by adipose tissue

<table>
<thead>
<tr>
<th>Molecule</th>
<th>Function/Effect</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASP</td>
<td>Promotes fat storage, inhibits lipolysis</td>
<td>12</td>
</tr>
<tr>
<td>Adipsin</td>
<td>Helps cleave the complement protein C3 into C3a and C3b ultimately to produce ASP</td>
<td>13</td>
</tr>
<tr>
<td>Adiponectin</td>
<td>Reduces hepatic glucose production while increasing muscle glucose utilization</td>
<td>12</td>
</tr>
<tr>
<td>Adipophillin</td>
<td>deposition and transport of cytosolic lipid droplets</td>
<td>14</td>
</tr>
<tr>
<td>Agouti protein</td>
<td>Regulator of energy homeostasis</td>
<td>15</td>
</tr>
<tr>
<td>Angiotensinogen</td>
<td>Regulator of blood pressure precursor of angiotensin II</td>
<td>16</td>
</tr>
<tr>
<td>Apo-E</td>
<td>Transport of cholesterol and other lipids between peripheral tissues and the liver</td>
<td>17</td>
</tr>
<tr>
<td>CETP</td>
<td>Facilitates the transfer of cholesteryl ester from HDL to apolipoprotein B-containing lipoproteins</td>
<td>18</td>
</tr>
<tr>
<td>FIAF</td>
<td>Regulation of metabolism, especially under fasting conditions</td>
<td>19</td>
</tr>
<tr>
<td>IL-1α</td>
<td>Regulation of fever and body heat</td>
<td>20</td>
</tr>
<tr>
<td>IL-6</td>
<td>Host defense, glucose and lipid metabolism</td>
<td>21</td>
</tr>
<tr>
<td>IL-6 sR</td>
<td>Augments the activity of IL-6</td>
<td>22</td>
</tr>
<tr>
<td>IGF-1</td>
<td>Stimulates cellular proliferation and mediates growth hormone</td>
<td>22,23</td>
</tr>
<tr>
<td>Leptin</td>
<td>Signals brain about adipose stores, energy expenditure</td>
<td>24</td>
</tr>
<tr>
<td>LPL</td>
<td>Hydrolyzes triglycerides VLDLs to free fatty acids for uptake into adipocytes</td>
<td>25</td>
</tr>
<tr>
<td>Metallothionein</td>
<td>Protection of fatty acids from oxidative damage</td>
<td>26</td>
</tr>
<tr>
<td>MIF</td>
<td>Immunoregulation and inflammation</td>
<td>27</td>
</tr>
<tr>
<td>NEFA</td>
<td>Elevated levels impair glucose uptake and increase liver gluconeogenesis</td>
<td>28</td>
</tr>
<tr>
<td>PAI-1</td>
<td>Regulation of the fibrinolytic system</td>
<td>29</td>
</tr>
<tr>
<td>PG12</td>
<td>Vasorelaxation and inflammation</td>
<td></td>
</tr>
<tr>
<td>PGF2a</td>
<td>Smooth muscle constriction, adipocyte differentiation</td>
<td>30</td>
</tr>
<tr>
<td>Resistin</td>
<td>Unknown</td>
<td>31</td>
</tr>
<tr>
<td>Retinol</td>
<td>Adipocyte is storage depot for Vitamin A</td>
<td>32</td>
</tr>
<tr>
<td>Retinol BP</td>
<td>Carrier protein for retinol</td>
<td>33</td>
</tr>
<tr>
<td>Steroids</td>
<td>Metabolism and secretion of sex steroids and glucocorticoids</td>
<td>34</td>
</tr>
<tr>
<td>TGFb</td>
<td>Controls PAI-I synthesis, cell growth and differentiation</td>
<td>35</td>
</tr>
<tr>
<td>TNFa</td>
<td>Partially responsible for insulin resistance in diabetes</td>
<td>36</td>
</tr>
<tr>
<td>TNFa sR-I</td>
<td>Autocrine and paracrine mediator of TNFa</td>
<td>36</td>
</tr>
<tr>
<td>TNFa sR-II</td>
<td>Autocrine and paracrine mediator of TNFa</td>
<td>36</td>
</tr>
</tbody>
</table>

Acylating stimulating protein (ASP), Adipsin, Adiponectin, Adipophillin, AdipoQ, Agouti protein, Angiotensinogen, Angiotensin II, Apolipoprotein E (Apo-E), Cholesteryl ester transfer protein (CETP), Fasting-induced adipose factor (FIAF), IL-1α interleukin 1 alpha, IL-6 (interleukin 6), IL-6 sR (interleukin 6 soluble receptor), Insulin-like growth factor-1 (IGF-1), Leptin, Lipoprotein lipase (LPL), Metallothionein, Macrophage inhibitory factor (MIF), Non-esterified fatty acids (NEFA), Plasminogen activator inhibitor-1 (PAI-1), PG12 prostacyclin, PGF2a, Resistin, Retinol, Retinol binding protein (Retinol BP), Steroids, TGFb (Transforming growth factor-b), Tissue factor, TNFa (Tumor necrosis factor a), TNFa sR-I (Tumor necrosis factor soluble receptor I), TNFa sR-II (Tumor necrosis factor soluble receptor II)

mRNA expression techniques, to be active in human adipocytes. Additionally, the activity of these plasma mediators has been positively correlated with BMI and decline dramatically with moderate amounts of weight loss.73-80 The end result is an overexpression of angiotensin II in obesity.

These findings would suggest that the metabolic effects of angiotensin II are important in obesity. Several authors have demonstrated that overproduction of aldosterone in obesity positively correlates with BMI,76,77,81,82 and that obesity is associated with volume expansion and sodium retention, even in moderate levels of obesity.74,82-85 In addition, the direct effects of angiotensin II on the sympathetic nervous system could be a cause of essential hypertension.86,87 Masuo et al86 followed 1,897 lean men
Table 2. Acute Phase reactants and inflammatory mediators in obesity, trauma, and ARDS

<table>
<thead>
<tr>
<th>Cytokine Marker</th>
<th>ARDS/ Trauma</th>
<th>Obesity</th>
<th>Weight Loss</th>
<th>References</th>
</tr>
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<tbody>
<tr>
<td>IL-1α</td>
<td>↑</td>
<td>↑</td>
<td>?</td>
<td>37-39</td>
</tr>
<tr>
<td>IL-1β</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
<td>37, 40</td>
</tr>
<tr>
<td>IL-1RA</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
<td>37, 40-41</td>
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<tr>
<td>IL-3</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
<td>37, 42</td>
</tr>
<tr>
<td>IL-6</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
<td>37, 43</td>
</tr>
<tr>
<td>IL-8</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>37, 44-45</td>
</tr>
<tr>
<td>TNF-</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
<td>37, 42</td>
</tr>
<tr>
<td>TNFsRA</td>
<td>↑</td>
<td>↑</td>
<td>?</td>
<td>37, 46</td>
</tr>
<tr>
<td>TGFbeta</td>
<td>↑</td>
<td>↑</td>
<td>?</td>
<td>37, 47</td>
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</tbody>
</table>

**Acute Phase Proteins**

<table>
<thead>
<tr>
<th>Protein</th>
<th>ARDS/ Trauma</th>
<th>Obesity</th>
<th>Weight Loss</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compliment C3</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
<td>37, 48</td>
</tr>
<tr>
<td>Haptoglobin</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
<td>37, 48</td>
</tr>
<tr>
<td>CRP</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
<td>37, 49-50</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
<td>37, 51-52</td>
</tr>
<tr>
<td>Serum amyloid A</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
<td>37, 53</td>
</tr>
<tr>
<td>Ceruloplasmin</td>
<td>↑</td>
<td>↑</td>
<td>?</td>
<td>37, 54</td>
</tr>
<tr>
<td>a1-anti-chymotrypsin</td>
<td>↑</td>
<td>↑</td>
<td>?</td>
<td>37, 55</td>
</tr>
<tr>
<td>LBP</td>
<td>↑</td>
<td>↑</td>
<td>?</td>
<td>56</td>
</tr>
<tr>
<td>AGP</td>
<td>↑</td>
<td>↑</td>
<td>?</td>
<td>56</td>
</tr>
<tr>
<td>PAI-1</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
<td>37, 51-52</td>
</tr>
</tbody>
</table>

**Cell Surface Receptors**

| CD14          | ↑            | ↑       | ↓           | 57-58      |
| CD14/CD16*    | ↑            | ↑       | ↓           | 57-58      |
| CD82          | ↓            | ↓       | ↑           | 58-59      |
| CD95          | ↑            | ↑       | ↓           | 59         |

**Other**

| vWF           | ↑            | ↑       | ↓           | 62         |
| FVIII         | ↑            | ↑       | ↓           | 62         |
| ESR           | ↑            | ↑       | ↓           | 60, 61     |

Lipopolysaccharide binding protein (LBP), α-Acid glycoprotein (AGP), CD95 (Fas Antigen), Plasminogen activator inhibitor-1 (PAI-1), Transforming growth factor-b (TGFb), Tumor necrosis factor α (TNFa), Tumor necrosis factor soluble receptor (TNFsRA), Von Willebrand's Factor vWF, Acute respiratory distress syndrome (ARDS)

*CD14/CD16 monocyt subset responsible for production of cytokines

over 10 years and found that plasma norepinephrine (NE) levels increased as BMI increased. The increase in NE levels directly correlated with rising blood pressure. The relative contribution between aldosterone-induced sodium retention and sympathetic over-activity in obese patients with hypertension still has to be elucidated (Figure 1).

**Tumor Necrosis Factor Alpha and Transforming Growth Factor Beta**

TNFα is one of the cardinal cytokines that mediate immune and inflammatory responses. It was originally thought to be produced only by macrophages and monocytes, and these cells continue to be heavily investigated.88,89 This is partly due to the strong association of TNFα with trauma, acute respiratory distress syndrome, multiple organ system failure, systemic inflammatory response syndrome (SIRS), septic shock and death.90-93 It has also been associated with apoptosis and the procoagulant state present in conditions of excess inflammation.89,94,95 Large amounts of TNFα are also present in obesity.

TNFα in obesity is produced by adipocytes throughout the body as seen in mRNA studies, but more abundantly by adipocytes in the waist-hip region.96 This is manifested as a mild correlation of serum TNFa with BMI, but strong correlation with
Figure 1. This figure illustrates the relationship between increased adipocyte mass, aldosterone and sympathetic tone as causes of hypertension in obesity.

waist-hip ratio. (The waist is measured at the narrowest point of the relaxed stomach while the hips are measured on the widest place). Both the adipocyte mRNA expression and serum TNFα levels are elevated in obesity and concurrently decrease with weight loss.

In trauma and other inflammatory conditions, TNFα is associated with several abnormalities in the hemolytic and fibrinolytic system. The abnormalities include increases in the serum levels of von Willebrand factor (vWF) and plasminogen activator inhibitor (PAI-1). In obesity, vWF correlates with BMI and waist circumference and decreases with weight loss. Levels of TNF expression also correlate with serum levels of vWF. While the exact mechanism has yet to be elucidated, it may be presumed that TNFα mediates vWF expression in obesity, in keeping with other states of chronic inflammation.

Serum levels of PAI-1, as with vWF, have also been found to correlate with TNF. Unlike vWF, which is produced in the liver, PAI-1 is produced by the adipocyte. TNF can directly induce the production of PAI-1, or it can influence its production through a TGF-β mediated pathway. TGFβ is elevated in acute inflammatory states, and levels of TGFβ positively correlate with BMI. With weight loss, both TGFβ and PAI-1 levels fall significantly. This may explain why chronic inflammation in obesity predisposes morbidly obese individuals to higher rates of thromboembolic phenomena.

Another relationship seen in acute inflammation and obesity is insulin resistance secondary to TNFα. There are many lines of evidence to support this hypothesis. TNFα, has been shown to induce insulin resistance in isolated cells, animals, and humans. Also, medication and dietary modifications improve insulin sensitivity, and this coincides with a decrease in TNFα and weight loss. The precise mechanism is related to TNFα receptor expression, as obese mouse models lacking either TNFα or its receptors do not exhibit significant insulin resistance. TNFα almost certainly plays a large part in obesity-associated insulin resistance (Figure 2). Future studies will investigate how much other insulin mediators that are elevated in obesity and decrease with weight loss such as enteroglucagon (glucagonlike peptide 1 [GLP-1]), and IL-1 (another acute phase reactant) interact with TNFα.

Figure 2. This figure demonstrates the effect of increased adipocyte mass on liver activation, as well as the possible mechanisms for increased cancer incidence, thrombotic events, hypertension, diabetes and dyslipidemia seen in obesity.
TNF and IL-6

In addition to inducing the production and secretion of TGFB, TNFα also induces the secretion of IL-6. IL-6 levels are elevated in obesity and correlate with the level of TNFα, waist-hip ratio (WHR) and BMI, and fall with weight loss. These two cytokines, in conjunction, are responsible for the dyslipidemia that is common in morbid obesity. Specifically, both IL-6 and TNFα correlate with the level of dyslipidemia, inhibit lipoprotein lipase (increasing VLDL and triglycerides), increase triglyceride secretion from the liver, and increase lipolysis (increasing free fatty acids), while TNFα alone stimulates hormone sensitive lipase, and down-regulates fatty acid binding protein and fatty acid synthase. All of these changes in lipid metabolism are reversible with weight loss (Figure 3).

Perhaps the most important aspect of IL-6 physiology is its induction of the acute phase response by the liver. The liver is responsible for the production of many of the acute phase proteins seen in trauma and sepsis. The most studied of these proteins are C-reactive protein (CRP), serum amyloid A (SAA), and fibrinogen.

CRP is a member of the pentraxin family of proteins and is secreted by the liver in response to IL-6 production in trauma, sepsis and other inflammatory conditions. It rises quickly in the face of inflammation and falls quickly with its resolution. It binds to Fc receptors to induce the secretion of pro- and anti-inflammatory cytokines, and to help the phagocytosis of bacteria. CRP activates complement, and down-regulates white blood cells adhesion molecules in response to sepsis and systemic inflammation. In morbid obesity, the level of CRP is positively correlated with the waist ratios, hip-waist ratios, and BMI. This relationship is unchanged in both "healthy" obese patients and in general population studies of adults and children.

With exercise and weight loss, the levels of CRP fall dramatically. Additionally, many of the same effects seen in trauma secondary to elevated levels of CRP, such as elevated cytokine levels, decreased expression of cell surface adhesive molecules, and increased expression of death receptors (apoptotic receptors), are seen in obesity. The altered expression of adhesive molecules such as L-selectin (CD62) and the increased expression of death receptors such as the fas antigen (CD95) secondary to inflammation could play a role in the increased incidence of wound infections and cancer in obesity. As white blood cells are unable to migrate to target sites, those that arrive are more susceptible to apoptosis (Figure 2).

IL-6 and TNF also promote the secretion of an additional sensitive acute phase protein elevated in trauma and sepsis, serum amyloid A (SAA) (Figure 3). SAA, together with CRP, provides us the ability to compare the inflammation present in obesity with other inflammatory states. In trauma and infection, CRP and SAA levels can rise from 200 to 500 fold for CRP and 500 to 2000 fold for SAA, while in morbid obesity they rise 20 fold for CRP and 10 fold for SAA (when compared to lean individuals). Furthermore, levels of SAA correlate with BMI, WHR, CRP and leptin. Perhaps more importantly, in inflammatory conditions such as trauma, sepsis, and rheumatoid arthritis, SAA has been shown to be responsible for the drop in HDL by replacing apolipoproteins A-1 and A-11 with...
SAA.157-161 This converts normal HDL (NHDL) into acute phase HDL (APHDL). APHDL is absorbed by macrophages more rapidly and is degraded faster.153,162-63 Thus, lower levels of HDL are seen in inflammatory conditions. This effect could explain the lower levels of HDL seen in obesity and offers an explanation for increased macrophage lipid uptake in the pathogenesis of atherosclerosis.52,156,164

Fibrinogen, like CRP and SAA, is an acute phase reactant produced in the liver, the production of which is controlled by IL-6.165-167 Fibrinogen is the main determinant of plasma viscosity and plays essential roles in blood rheology, platelet aggregation, and endothelial function.168-170 Elevated levels have been found in obesity and correlate with CRP, SAA, BMI and WHR in most studies.171-180 Furthermore, fibrinogen levels decline with weight loss greater than 10%.50,173,178,180 Certainly, the higher levels of fibrinogen, von Willebrand factor and PAI outlined here, when combined with the elevated levels of Factor VII and Factor VIII, predispose obese patients to a higher risk of thromboembolic complications.61

Treatment of Obesity

The causes of obesity are multifactorial. Current treatment options for mild obesity (BMI<35) include diet and exercise. However, for the majority of patients with a BMI >35, durable non-surgical weight loss has proved unsuccessful for many individuals. It is for these reasons that the NIH recommended in 1991 and in 1998 that surgical treatment be considered for patients with a BMI >40 or for patients with BMI >35 and co-morbid conditions who have failed supervised weight loss attempts.181,182 Weight loss surgery has been shown to eliminate between 85% and 95% of all co-morbid conditions associated with obesity with an acceptable low morbidity.183-5 The success of weight loss surgery is related to the anti-inflammatory effects of sustained weight loss. Many of the above studies determined that weight loss was associated with resolution of clinical as well as physiologic phenomena. While many aspects of bariatric physiology remain unclear, there appears to be a strong association between obesity and inflammation, thereby rendering obesity a chronic inflammatory state. Chronic inflammation could account for many of the detrimental effects of obesity in these patients. Future studies should further investigate this critical relationship (whether it is in the causal pathway or merely associative) in order to increase our understanding of both the patterns of inflammatory response in the context of obesity and its effect on body physiology.

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Cottam et al


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