The Answer to Why Some Are Obese but Healthy?!

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Abstract

Obesity is a complex issue involving both physical and metabolic dysfunction. Some obese individuals are spared from the unfavorable metabolic disturbances often seen in that condition. Such individuals are referred to as healthy obese persons who constitute a considerable proportion of the obese group of subjects. The possible roles of several important adipokines that are studied in this regard are presented in this communication. The importance of such group of obese individuals and other variant such as metabolically obese with normal body weight status and other challenges faced is pointed out both for clinical and research purposes.

Keywords

Obesity, Healthy obesity, Metabolic disturbances, Adipokines, Inflammation

Obesity and Favorable Metabolic Profile

Human obesity has been documented long back [1] WAT has a role in the regulation of whole-body energy metabolism and its endocrine function has a critical role in the development of obesity and its metabolic and cardiovascular complications by secreting cytokines/adipokines in distorted proportions. In obese individuals, monocyte and B and T lymphocyte infiltration into the adipose tissue results in low-grade inflammatory state associated with a rise in circulating C-reactive protein (CRP) which could be used as a marker for the development of type 2 diabetes mellitus (T2DM) and insulin resistance (IR) [2-4]. However, it should be noted that obesity itself will not lead to the development of IR but, the adipose tissue inflammatory condition is the culprit in metabolic disorders of humans [2]. This fact is further supported by a study on metabolically normal obese postmenopausal women who had exhibited lower CRP and alpha-1 antitrypsin levels suggesting a protective role of these inflammatory markers against cardiometabolic risks [5].

Recent advances in obesity research deny some of the generalizations made commonly on excess body weight and health. For example, just the extra body fat does not always result in higher health risks or the lower body fat levels provide risk free health status is a very appropriate one to consider [6]. Interestingly, some obese persons with elevated body fat mass are free from cardiovascular and metabolic risks. They exhibit a healthy inflammatory status, good lipid profile and less insulin resistance with no signs of hypertension. Such individuals are at a lower risk as compared to metabolically unhealthy obese (MUHO) individuals and hence called metabolically healthy obese (MHO) persons [7, 8]. The black obese people and the Japanese sumo wrestlers who have very little visceral fat and heavy muscle mass have a greater tendency of being metabolically healthy when compared with their respective control subjects [9, 10]. Another study by...
Meigs et al., involving nearly 3000 men and women has shown that the MHO subjects were at no higher risk of developing cardiovascular disease or T2DM, when compared to healthy normal weight individuals [11]. In one more work, Albrink and Meigs [12] have reported that many of their obese subjects had healthy levels of triglycerides. A study on liver enzymes in MHO postmenopausal women has shown healthy levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST) and gamma-glutamyltransferase (GGT) [13]. Reduced amounts of liver enzymes, especially lower circulating ALT may represent lower hepatic insulin resistance and reduced liver fat content that may be partly responsible for the favorable metabolic profile of MHO individuals. Evidence also from animal studies in which healthy obese mice lacked a protein called collagen VI was metabolically much better without developing inflammation or IR than their counterpart that had the collagen VI also supports the view on MHO [14].

Available studies report that 20-30% of such obese individuals appear to be in metabolically healthy category [9, 11, 15, 16]. These individuals have been differently referred to as ‘metabolically normal obese’ (MNO), ‘metabolically healthy but obese’ (MHO), ‘obese but metabolically normal’ (OMN) or as having metabolically uncomplicated obesity or ‘Healthy Obese’ subtype [17]. However, there is no consistent method to define MHO individuals [18]. Though, some suggestions have been made [9, 19, 20], it should be noted that the criteria could be modified and that the cut-off points should be refined particularly for blood pressure, waist circumference, fasting glucose and eventually post-load glycemia. On the other hand, lean individuals can also develop acute inflammation-induced insulin resistance, even without having extra body fat. This subgroup is referred to as metabolically obese but normal weight (MONW) type [9]. A recent study has reported that a lean insulin-resistant subject may have elevated pro-inflammatory markers such as MCP-1, IL-6 and resistin than an overweight, insulin sensitive subject [21]. The characteristics of these different groups are shown in table 1.

### Prevalence

MHO individuals represent a very challenging subgroup. Wildman and his colleagues in their study have reported that 51.3% of overweight and 31.7% of obese adults were MHO [9]. Others have reported a prevalence from 6% to 40% in different overweight and obese populations [11, 20, 22, 23]. Data available from a limited number of studies from the West shows the prevalence of MHO ranging from 11-40% whereas the prevalence of MONW is about 5-45% [24]. A recent study from Korea involving over 5000 subjects [25] also asserts this view and it reports that 48% of the lesser age and about 13% of the older age group is MHO. The major cause of such a wide difference may be due to differences in study design and how the metabolic health is defined. However, no such data is available as yet for Asian countries.

### What Contributes to MHO?

What contributes to this phenomenon of MHO is not clear but a significant role for adipokines has been suggested. However, some reports on the possible role of leptin, adiponectin, and resistin in MHO have indicated that higher leptin levels, leptin/adiponectin ratio, and lower adiponectin contribute to the increased risk of hypertension in MHO both in children and adolescents and elevated adiponectin level among obese women could be presumably provide a favorable metabolic profile [26, 27]. A few studies have shown that circulating adipokines such as chemerin and retinol-binding protein-4 were significantly low in MHO subjects as compared to metabolically unhealthy obese (MUO) individuals [28]. So also, in MHO individuals circulating levels of total adiponectin or high molecular weight adiponectin [28, 29] similar to lean healthy (LH) individuals and increased levels as compared MUO individuals have been reported. Phillips et al. [30] have recently shown that MHO and LH individuals have significantly lower concentrations of plasminogen activator inhibitor-1, as well as higher adiponectin levels, compared with their MUO counterpart. It was also found that MHO individuals had lower blood levels of fetuin-A, (a hepatokine) that was associated with improved insulin sensitivity and glucose homeostasis as compared with MUO individuals [28, 31].

Therefore, understanding the interplay of adipokines is vital that might explain why some obese individuals develop complications, and others do not. Adipose tissue, now established as the largest endocrine organ secretes various bioactive molecules called adipokines that have many different biological effects [32]. It secretes leptin, adiponectin, resistin, interleukin-6 (IL-6), plasminogen activator inhibitor-1 (PAI-1) and monocyte chemotactic protein-1 (MCP-1) and

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**Table 1: Clinical and diagnostic characteristics of the sub-types of obesity as compared to a normal healthy individual [71].**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Metabolically healthy &amp; normal weight (MNW)</th>
<th>Metabolically unhealthy Obese (MUO)</th>
<th>Metabolically healthy obese (MHO)</th>
<th>Metabolically obese normal weight (MONW)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI</td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Total fat mass</td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
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<tr>
<td>Visceral fat</td>
<td>↓</td>
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<tr>
<td>Liver fat</td>
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<tr>
<td>Muscle fat</td>
<td>↓</td>
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<tr>
<td>Triglycerides</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
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<tr>
<td>HDL Cholesterol</td>
<td>↑</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Lean body mass</td>
<td>↑</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Insulin resistance</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
<td>↑</td>
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<tr>
<td>Insulin secretion</td>
<td>Normal</td>
<td>↑</td>
<td>Normal</td>
<td>↑</td>
</tr>
<tr>
<td>Onset of obesity</td>
<td>---</td>
<td>Late onset</td>
<td>Early onset</td>
<td>Late onset</td>
</tr>
</tbody>
</table>
many other cytokines. Adipokines are grouped into hormones, growth factors, angiogenic factors, and cytokines. Of all the adipokines, leptin, adiponectin, resistin, monocytes, and macrophage chemotactic protein 1 (chemokine [C-C motif] ligand [CCL]-2), interleukin (IL)-6, IL-1β, tumor-necrosis factor (TNF), anti-inflammatory IL-10, and transforming growth factor (TGF)-β are often studied ones [33]. A summary of the functions of these adipokines in health and changes in their levels in obesity is given in table 2.

<table>
<thead>
<tr>
<th>Adipokine</th>
<th>Major functions</th>
<th>Changes in obese individuals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leptin</td>
<td>Energy expenditure.</td>
<td>Increased adipocytes expression/secretion, leptin resistance, hyperleptinemia, Inflammatory cell activation.</td>
</tr>
<tr>
<td>Adiponectin</td>
<td>Insulin sensitivity, fatty acid oxidation, adipose tissue glucose uptake, adipogenesis, glucose metabolism.</td>
<td>Free fatty acid uptake, glucose secretion in the liver, anti-inflammatory, antiatherogenic, and antidiabetic actions. Decreased expression and secretion in adipose tissue and serum levels.</td>
</tr>
<tr>
<td>Resistin</td>
<td>Insulin resistance, proinflammatory cytokines secretion, adhesion molecules.</td>
<td>Increased serum levels in mice. Controversial results in humans.</td>
</tr>
<tr>
<td>TNF</td>
<td>Inflammation, lipolysis in adipose tissue.</td>
<td>Insulin signaling. Increased expression and secretion in adipose tissue.</td>
</tr>
<tr>
<td>IL-6</td>
<td>Insulin signaling, release of free fatty acids (adipose tissue).</td>
<td>Metabolic actions. Increased expression and secretion in adipose tissue and serum levels.</td>
</tr>
<tr>
<td>CCL2</td>
<td>Macrophage infiltration and adipose tissue inflammation.</td>
<td>Increased serum levels and expression in adipose tissue.</td>
</tr>
<tr>
<td>IL-10</td>
<td>Macrophage activity, proinflammatory cytokine synthesis.</td>
<td>Increased serum levels but, decreased in metabolic syndrome (in women).</td>
</tr>
<tr>
<td>TGFβ</td>
<td>Growth and activation of immune cells, macrophage activation, T- and B-cell activation.</td>
<td>Increased both in humans and animals.</td>
</tr>
</tbody>
</table>

Note: TNF: tumor-necrosis factor; IL: interleukin; CCL: chemokine (C-C motif) ligand; TGF: transforming growth factor.

Role of Some Important Adipokines

**Leptin**

Leptin is mainly secreted by subcutaneous adipose tissue. It plays an important role in the regulation of food intake and also promotes energy expenditure. It affects heat production, lipid metabolism, blood cells production, activity of the ovary and β-cell function [33, 34]. Obesity is closely related to leptin resistance leading to increased blood levels of leptin [35]. Leptin controls the expression of pro-inflammatory cytokines in macrophages and T cells and induces inflammation. Interactions between leptin and inflammation play a vital role in maintaining chronic inflammatory state in obesity which leads to more and more secretion of leptin [33].

**Adiponectin**

Like leptin, adiponectin is primarily secreted in subcutaneous adipose tissue. Adiponectin has antidiabetic, anti-inflammatory, antiatherogenic (pro-angiogenic) and anti-apoptotic effects. It also limits the infiltration of monocytes/macrophages into adipose tissue and their conversion into foam cells in the vessel wall providing the anti-inflammatory and antiatherogenic effects. Additionally, adiponectin also increases insulin sensitivity, fatty acid oxidation and decreases secretion of glucose from liver, increases glucose uptake, and adipogenesis [22, 33, 36]. Adiponectin also promotes glucose metabolism and accelerates the oxidation of free fatty acids in the muscle [37, 38]. In total these are favorable effects of adiponectin to prevent the negative metabolic and cardiovascular effects in obesity.

There is an inverse relationship between circulating adiponectin level and body mass index (BMI), waist circumference, body fat percentage and insulin resistance. Adiponectin concentration is reduced in diabetes, hypertension and coronary arterial disease. Such an observation of low adiponectin levels is made among the Pima Indians, who have high prevalence of Type 2 Diabetes Mellitus (2TDM), while subjects with high adiponectin levels were found to be less likely to develop diabetes than those with low concentrations. This finding indicates the protective effect of adiponectin in such individuals with greater tendency of developing diabetes [39]. Similar studies on obese African Americans with hyperadiponectinemia also had shown a healthier metabolic profile, including increased high-density lipid cholesterol, lower insulin levels, smaller waist circumference, lower insulin levels and favorable inflammatory profile as compared to those without hyperadiponectinemia [29, 40].

Although it has been shown previously that serum leptin correlates positively with BMI and body fat %, its level in the MHO group was similar to that of the metabolically unhealthy group [41]. Adiponectin and leptin are closely involved in fat...
metabolism and act as important mediators of atherosclerosis in obesity. Therefore, when leptin to adiponectin ratio was considered, it was less in the MHO subjects as compared to the metabolically unhealthy group. This ratio could therefore, be an indirect marker to evaluate metabolic syndrome and atherosclerosis in obese T2DM patients [42, 43].

**Interleukin-10 (IL-10)**

Interleukin-10 (IL-10) is secreted by several different tissues and has multiple roles. It regulates insulin signaling and lipid metabolism in peripheral tissues along with its inflammation and host defense role [51]. Obesity, glucose intolerance and insulin resistance is positively correlated with increased IL-6 and can predict the development of T2DM, metabolic syndrome, and cardiovascular disease [47]. Weight loss reduces blood levels of IL-6 and also its expression by adipose tissue. Comparable IL-6 and CRP serum levels have been reported in lean and MHO subjects, but were less than the unhealthy obese [52, 53].

**Other adipokines**

Chemerin has important roles in inflammation, metabolism and acts as a link between chronic inflammation, obesity and obesity associated co-morbidities. Interestingly, chemerin has been assigned both a proinflammatory and anti-inflammatory actions [56, 57].

Orosomucoid modulates the immune responses from excessive inflammation and metabolic disturbances and thus has a protective role on adipose tissue [52, 57, 58]. Its secretion from the adipocytes markedly increases in inflammatory and metabolic stress conditions and also by TNF-α, insulin, glucose and free fatty acids [59]. It is believed that there is a positive correlation between circulating orosomucoid levels and BMI and body fat mass rather than the metabolic status of the individual [58].

Two other adipokines namely, omentin and vaspin have anti-inflammatory effects that will result in improving IR while lipocalin 2 and visfatin are pro-inflammatory adipokines that promotes TNF expression in the adipose tissue [60]. More recently, it has been shown that plasminogen activator inhibitor-1 (PAI-1) levels are high in obese subjects, which has been further substantiated by several interventional studies where PAI-1 levels reduced significantly after obese people lost weight [61].

**Challenges**

The following challenges are to be addressed regarding obesity.

A) A proper clinical classification of health risk in obesity,

B) Identification and treatment prioritization of obese individuals at highest risk of developing disease and early mortality [18]. Furthermore, it is now believed that all the MHO individuals may not be in good health and it is not certain for how long they maintain good health status during their entire life time! Appleton et al., reported that the MHO phenotype was stable for 67% of their study participants over a 10-year period [62], suggesting that MHO individuals may have greater resistance to the development of obesity-related complications and in contrast, another study has suggested that excess body weight compromises long-term health [63].

Several other studies have suggested an increased risk for long-term adverse effects including cardiometabolic complications even in the absence of metabolic abnormalities in obese persons [64]. Dobson et al. [65] have hypothesized that metabolically unhealthy individuals irrespective of their BMI, would have adverse levels of ectopic fat (visceral and liver fat deposition) and myocardial dysfunction compared with MHO individuals. Morkedal et al. [66] have revealed that there is no relationship between acute myocardial infarction and MHO.
subjects, but, have established an association with increased risk for heart failure in MHO subjects particularly for long-lasting or severe obesity. Furthermore, excess accumulation of ectopic fat in liver, skeletal muscle, and pancreas is known to contribute to metabolic disturbances [67]. For example, Ogorodnikova and his co-workers have reported that MHO women had intermediate levels of epicardial, pericardial and hepatic fat as compared to lean healthy and MÜO women and were associated with insulin resistance [68].

Another question to answer is, should such MHO individuals lose body weight? However, different opinions have been put forth in this regard [6, 69, 70]. Otherwise, to treat all obese patients with the idea of ‘one size fits all’ may be counterproductive.

**Conclusion**

The pathogenesis of metabolic disorders associated with obesity is closely related to adipokine secretion pattern from adipose tissue. Adipokines are important biomolecules that play a major part in inflammation and IR in obesity. MHO individuals being free from obesity related co-morbidities have become the target of further research. The mechanisms of favorable metabolic profile in MHO individuals thoroughly investigated can be very helpful to understand the protective factors that lead to metabolic imbalance and co-morbidities in obesity.

Of all the adipokines, it is important to note that adiponectin is a feasible and lucrative therapeutic target as it has anti-inflammatory and vascular protective effects. Several major pharmacological approaches such as (i) agents that increase the circulating concentrations of adiponectin, (ii) agents that increase adiponectin receptor expression, and (iii) agonists of the adiponectin receptor which induce signaling pathways of adiponectin receptors are currently being employed for its evaluation [71]. However, adiponectin research is quite recent and is progressing in the right direction. It would take another 1-2 decade to come out with possible conclusive reports from such reports as per the expert’s opinion in the field. Sometimes the inflow of information from such research is also complex and confusing that one should be extra careful and wise in accepting the findings. But, science keeps growing and one day someone will hit the target, hopefully.

In conclusion, it has been suggested that obesity for some individuals is not a serious health risk factor and might even be an advantage. Several studies on obesity have concluded that, a) there are some groups of individuals who are genetically programmed to carry extra fat and they can be considered healthy as long as they can maintain good cardiovascular health, b) there are mild or moderate benefits of obesity which is poorly understood or entirely unknown and therefore one needs to be very cautious in their weight loss programs [72]. Finally, it can be stated that the subgroups of obesity can make things interesting in three important areas; i) impact of losing weight by these individuals, ii) inclusion of these groups in obesity research and its impact on the outcome of statistical analysis and iii) including them in medical education and clinical evaluation to address the need for better characterization of such patients [72].

**References**


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