Narrative Review

Understanding Obesity: The Role of Adipose Tissue Microenvironment and the Gut Microbiome

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Abstract

The prevalence of obesity has more than doubled globally over the past few decades, with a 12-fold rise in extreme levels. Obesity, with its multiple complications, remains a major ongoing challenge for health-care professionals, as highlighted by the COVID-19 pandemic, where people with obesity had poorer outcomes. In this article, we review advances in our understanding of the pathophysiology underlying obesity, with a focus on the immune system and its interaction with both the adipose tissue organ and the gut microbiome. As our understanding of the causes and effects of obesity improves, opportunities should emerge, underpinned by rigorous laboratory and clinical research, to both better prevent and treat this global epidemic.

Keywords: Adipose tissue, gut microbiome, immune cells, inflammation, obesity

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INTRODUCTION

Obesity, which is most commonly measured as a body mass index (BMI) >30, is defined as "a multicausal chronic disease recognized across the life span resulting from long-term positive energy balance with development of excess adiposity that over time leads to structural abnormalities, physiological derangements and functional impairments."[1-3] Over the past few decades, the rates of obesity have shown a dramatic upward trend globally. According to the World Health Organization, in 2016, about 650 million people were obese, which corresponds to about 13% of the world's population. In addition, the prevalence of childhood and adolescent obesity is also increasing.[4]

Obesity and its complications remain a challenge for clinicians. This has also been highlighted by the COVID-19 pandemic. A recent systematic review showed that obesity was associated with an increased risk of acquiring COVID-19 and higher rates of hospitalization, intensive care unit admission and mortality.[5] In general, the options for treating obesity include dietary, behavioral and physical activity intervention as well as pharmacotherapy and bariatric surgery.[6] The degree of weight loss and its durability and translation into improved health outcomes vary according to the type of intervention used and the individual characteristics of a patient. However, trial data on long-term results of weight-loss interventions are currently limited.[7] It is only through a fuller understanding of the pathophysiology of obesity that we will be able to devise effective preventive and therapeutic measures.

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In this article, we explore some aspects of the altered physiology in obesity with a particular focus on the adipose tissue microenvironment, the gut microbiome and their interactions. To inform this article, a literature search was carried out on PubMed using the following words or MeSH terms: "obesity," "pathophysiology," "pathogenesis," "mechanisms," "BMI," "the gut microbiome," "weight loss," "adipose tissue," "weight regain," "chronic inflammation" and "insulin resistance." The search was carried out between April 1, 2019, and December 31, 2019, and was limited to articles published in the English language between 1990 and 2019. The Cochrane Library database was also searched for relevant articles.

PATHOPHYSIOLOGY OF OBESITY

Genetic predisposition and environmental factors play an important role in the pathogenesis of obesity [Figure 1]. To study the genetic basis of obesity, genome-wide association studies, genome-wide linkage studies and candidate gene analysis have been carried out, and about 500 genes have been linked to obesity.[8] In terms of environmental factors, an abundance of high-calorie foods and a sedentary lifestyle have been commonly incriminated. For a long time, obesity was believed to simply be a result of calorie intake being in excess of calorie expenditure. However, evidence from ongoing research shows that the mechanisms underlying obesity are far more complex. Obesity is associated with a dysregulation of energy homeostasis rather than a passive fat deposition.[9] Two key areas of focus in recent research on the pathophysiology of obesity are the adipose tissue microenvironment and the gut microbiome. In the following sections, we will explore them further.

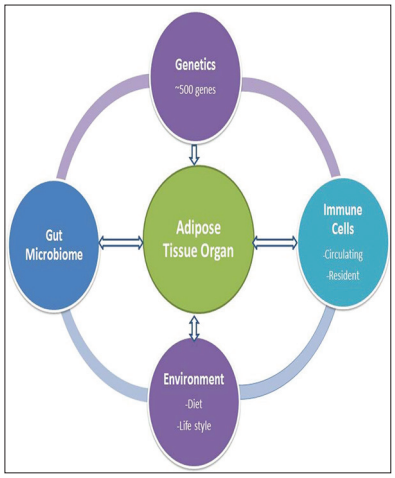

Figure 1: Key determinants of obesity

THE ADIPOSE TISSUE MICROENVIRONMENT

Brown adipose tissue (BAT) and white adipose tissue (WAT) are two types of adipose tissue present in humans. While BAT is primarily present at birth and plays an important role in thermogenesis, adult fat stores consist mostly of WAT. Nonetheless, studies have shown that in adults, BAT is located mainly in the supraclavicular region, with relatively small amounts present in perivascular and perivisceral distributions.[10] In terms of its significance, BAT activity has been shown to play an important role in metabolism and is associated with lowering the levels of blood glucose, triglycerides and free fatty acids. Obesity is associated with a reduced BAT activity, which in turn could promote insulin resistance and dyslipidemia. Accordingly, enhancing BAT activity, through intermittent cold exposure, β_3-adrenergic receptor agonists and exercise, has been considered as a potential therapeutic target for obesity. However, BAT activation has not been shown to result in clinically significant weight loss, and thus further studies are required to establish the viability of BAT activation as a therapeutic goal.[11]

In contrast to BAT, major deposits of WAT are present in the abdominal and gluteofemoral subcutaneous tissues and surrounding the viscera.[12] The visceral adipose tissue locations include omental, mesenteric, retroperitoneal, perirenal, gonadal and pericardial.[13] Excess central (and especially visceral) adipose tissue deposition is associated with a higher risk of cardiometabolic complications of obesity as compared to peripheral (gluteofemoral) adiposity.[14] WAT is now considered a major endocrine organ that contains a complex array of other cells including endothelial cells, fibroblasts, macrophages, B-cells, neutrophils, mast cells, $CD4^+$ and $CD8^+$ T-cells, type 1 T-helper (Th1) cells, type 2 T-helper (Th2) cells, regulatory T-cells (Tregs) and natural killer T (NKT) cells.[15] Several hormones and other chemical substances are secreted by the cells in WAT. Some of the examples include adiponectin, leptin, resistin, interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α).[16] All of these have an extensive range of physiological actions in the body including a significant role in the immunoregulatory and inflammatory pathways.

Immune dysregulation and chronic inflammation in obesity

Expansion of WAT in people with obesity is associated with dysregulation of its immune pathways and a state of low-grade, chronic inflammation. Complex interactions between immune cells in obese adipose tissue result not only in persistent weight gain and inflammation but

also in systemic insulin resistance.[15] Insulin resistance is characterized by the peripheral tissues having lower sensitivity to insulin, and this is an important feature of type 2 diabetes mellitus (T2DM) and metabolic syndrome.[17] Two key players involved in the adipose tissue inflammatory and immune networks are the macrophages and NKT cells.

Macrophages

Macrophages constitute a dominant cell population in the obese adipose tissue. They are mainly recruited from circulating monocytes and play a crucial role in adipose tissue inflammation and insulin resistance. The phenotype and function of macrophages vary in lean and obese adipose tissue. In lean adipose tissue, the predominant type of macrophages is alternatively activated macrophages (M2), which have anti-inflammatory properties and protect against obesity and insulin resistance [Figure 2]. M2 macrophages express CD206, CD209 and CD301 antigens and secrete anti-inflammatory cytokine IL-10. Conversely, in obese adipose tissue, classically activated macrophages (M1) predominate, and they express F4/80, CD11b and CD11c antigens. M1 macrophages secrete pro-inflammatory cytokines such as IL-1β, MCP-1, TNF-α and IL-6, and thus promote inflammation and insulin resistance.

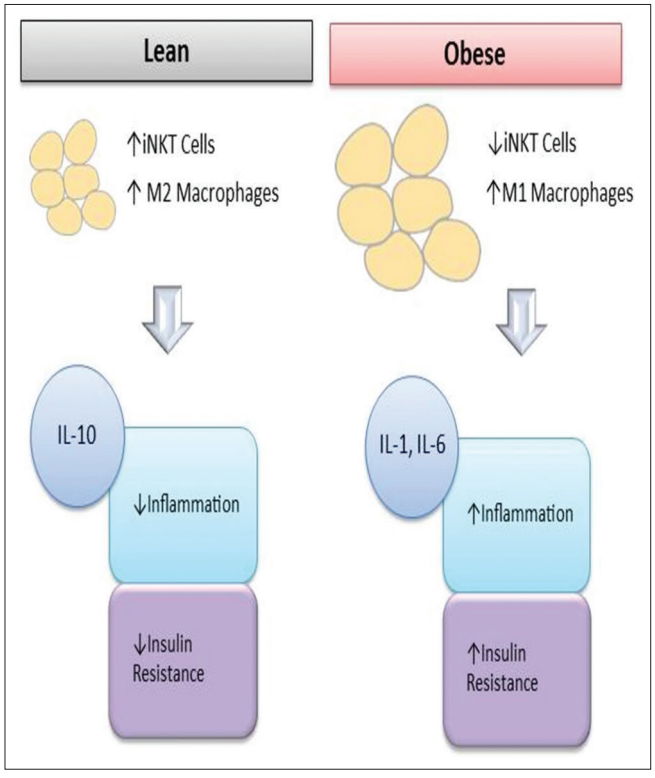

Figure 2: Changes in the adipose tissue microenvironment in lean versus obese setting

It is worth noting that *in vivo* studies have demonstrated the ability of adipose tissue macrophages to simultaneously express M1 and M2 antigens and secrete both pro- and anti-inflammatory factors. In addition, their ability to switch between phenotypes has also been shown. Therefore, the presence of M1/M2 phenotypes is better considered as a continuum rather than two completely different states.[18,19] Studies in obese mice have shown that certain macrophage-related genes such as ADAM8, MCP-1 and MAC-1 are upregulated in WAT, indicating an increase in the activity of macrophages. Triggers for the activation of macrophages are not yet fully understood, but several role players have been described. These include complement C3 as well as hormones, cytokines and FFAs secreted by adipocytes.[17]

Adiponectin produced by adipocytes contributes to the polarization of macrophages toward the anti-inflammatory M2 phenotype. The effects of adiponectin are mediated by activation of AdipoR1 and AdipoR2 receptors and their downstream signaling pathways. The development of obesity is associated with decreased adiponectin activity.[20] The polarization of macrophages toward the M2 phenotype is also promoted by the adipose tissue Th2 cells via IL-4 and IL-13 cytokines. However, with adipose tissue expansion in obesity, the number of Th1 cells predominates and they promote the polarization of macrophages toward pro-inflammatory M1 phenotype through interferon-γ and TNF-α.[15] Studies have also shown that nutritional fatty acids play a role in inflammatory signaling in macrophages and adipocytes through toll-like receptor 4 (TLR4).[21] Another important regulator of macrophages and their associated inflammatory and immune pathways in the adipose tissue microenvironment are the NKT cells.

Natural killer T-cells

These are a type of cytotoxic T-cells, and its two subclasses include type 1 or invariant NKT (iNKT) cells and type 2 or variant NKT cells. Both the varieties appear to play an opposing yet significant role in adipose tissue inflammation. In addition, they are also involved in other diseases such as infections, autoimmune conditions and cancer.[22] Studies have shown an inverse correlation between the number of iNKT cells and total adipose tissue mass.[23,24] With the expansion of adipose tissue in obesity, the number of iNKT cells is reduced; weight loss may result in the restoration of iNKT cell numbers. Cells of this variant are capable of producing anti-inflammatory cytokines such as IL-10 and may have positive effects on fat cells and metabolism. Through IL-10, they can polarize macrophages toward the M2 phenotype, which can, in turn, lead to further anti-inflammatory cytokine production and decreased

insulin resistance.[24,25] Conversely, a lower number of iNKT cells in obese adipose tissue are associated with an increase in macrophages of the M1 phenotype, which promote inflammation.

Other immune cells in the adipose tissue

In addition to macrophages and NKT cells, other players in the adipose tissue microenvironment have also been identified. As mentioned earlier, they include Th1 and Th2 cells, $CD4^+$ and $CD8^+$ T-cells, Tregs, B-cells, mast cells and neutrophils. Most Th cells are CD4+ and their roles have briefly been described in the previous section. Tregs play an anti-inflammatory role and their numbers in adipose tissue are decreased in obesity. CD8+ T- and B-cells, which are cytotoxic and antibody-producing immune cells, respectively, are increased in obese adipose tissue and cause the polarization of macrophages toward pro-inflammatory M1 phenotype. Mast cells secrete pro- and anti-inflammatory cytokines and play a role in the modulation of insulin resistance. Neutrophils play a crucial role in the initiation of the acute inflammatory response in the body. This suggests their potential role in adipose tissue inflammation; however, studies have reported inconsistent findings and whether neutrophil recruitment is the primary event of adipose tissue inflammation remains unclear.[18] It is worth emphasizing that an improved understanding of immune cell–cytokine cross-talk with adipose tissue metabolism can potentially lead to the identification of novel therapeutic targets and strategies for addressing obesity.

THE GUT AND THE GUT MICROBIOME

The gastrointestinal tract is inhabited by the gut microbiome and plays a crucial role in the regulation of energy homeostasis. Part of this role is mediated by gut hormones including cholecystokinin, peptide YY (PYY) and incretins, which include glucose-dependent insulinotropic peptide (GIP) and glucagon-like peptide-1 (GLP-1). PYY is secreted postprandially by the intestinal L-cells and acts on the Y2 receptors. It reduces gastric acid secretion, decreases gastrointestinal motility and increases satiety. It also acts on the neurons in the hypothalamic arcuate nucleus and nucleus tractus solitarius in the brainstem to increase satiety.[26]

Both GIP and GLPI-1 are released in response to the dietary stimuli and increase pancreatic beta-cell proliferation and insulin secretion. GLP-1 also has additional effects such as delayed gastric emptying, early satiety and inhibition of glucagon secretion. In addition to the gut and pancreas, GLP-1 receptors are found in other tissues of the body such as the heart, kidneys and brain.[27] In the brain, GLP-1 stimulates the satiety centers especially in the arcuate nucleus, paraventricular nucleus, nucleus tractus solitarius and area postrema.[26] In addition, studies in mice have suggested the role of the gut microbiota in modulating GLP-1 secretion.[28] Therefore, GLP-1 and its interactions are of great therapeutic interest. The development of GLP-1 agonists (such as liraglutide, dulaglutide and semaglutide) has proven to be an exciting milestone in the treatment of T2DM and obesity. In addition to improving glycemic control, GLP-1 agonists are useful for weight loss in patients with or without diabetes.[29,30] They appear to have anti-inflammatory properties mediated through a direct effect on immune cells both within the circulating and the tissue-resident immune systems – including the adipose tissue immune organ. The anti-inflammatory actions of GLP-1 agonists are independent of the changes that occur in weight or HbA1c.[31] Further studies are needed to thoroughly understand and exploit their role in this domain.

The gut microbiome in obesity

Another emerging area in obesity pathophysiology is the gut microbiome, which is an active area of research with different studies showing its association with various diseases including obesity and metabolic syndrome.[32] The role of the gut microbiome in influencing the host metabolism and inflammation and its close links to the obese tissue microenvironment have surfaced as an exciting new dimension to our understanding of the obesity pathophysiology.[33] Furthermore, the interactions of the gut–brain axis and microbiome have also been described.[26] The composition of the microbiota is influenced by various factors such as the host age, gender, genetics, BMI, diet and antibiotic use.[34,35] On the therapeutic front, fecal microbiota transplantation (FMT) has been proven to be an effective treatment against *Clostridioides difficile* infection and its role in other disorders including obesity is under investigation. One study showed that peripheral insulin sensitivity was transiently increased in individuals with obesity who received FMT from lean donors.[36,37]

The adult human gut microbiome consists of roughly 10–100 billion microorganisms weighing approximately 1.5 kg, with their highest density being in the colon. The primary gut residents are *Firmicutes*, *Bacteroidetes*, *Actinobacteria*, *Proteobacteria*, *Fusobacteria*, *Verrucomicrobia* and *Cyanobacteria*,[35,38] although small populations of archdeans, eukaryotes and viruses are also present. *Firmicutes* (Gram positive) and *Bacteroidetes* (Gram negative) are the predominant gut microbial phyla.[39-41] Obesity is associated with a change in the composition of gut

microbiota of the affected people compared with their normal-weight counterparts.[34,35,42] However, studies have reported conflicting results about the relative proportions of various microorganisms. For example, some studies have found that the gut *Firmicutes*/*Bacteroidetes* ratio is increased in people with obesity,[35,43-45] whereas others have reported weight loss to be associated with an increase in the *Bacteroidetes* population.[46,47] Similarly, some studies have shown an increased population of *Actinobacteria* and a lower proportion of *Bacteroidetes* but no significant change in *Firmicutes* population in obese individuals,[48,49] yet others did not find a correlation between BMI and the *Firmicutes*/*Bacteroidetes* ratio. In addition, whether the change in gut microbiota composition is a cause or effect of obesity remains unclear. Nevertheless, there is evidence to support that gut microbiota plays a significant role in the regulation of energy balance and adiposity and that high-fat diet intake can alter the composition of gut microbiota. However, the precise underlying mechanisms that link the microbiota to the causation of obesity have not been fully elucidated yet.[35] Possible mechanisms include "energy harvesting" and "metabolic endotoxemia," to name a few.

The microbiome and energy harvesting

Fermentation of dietary carbohydrates by the microbial hydrolases in the gut results in the generation of short-chain fatty acids (SCFAs), mainly butyrate, propionate and acetate.[50] SCFAs serve as a source of energy for the host. According to the energy harvesting hypothesis, the microbiota in people with obesity is more efficient at extracting energy from the diet, subsequently leading to enhanced adipose tissue deposition.[35] However, studies have lacked consistency in proving energy harvesting as a principal cause of obesity. In addition, it has been observed that SCFAs modulate the secretion of PYY and GLP-1.[50] This suggests that they instead might have a protective role against obesity.

The microbiome and metabolic endotoxemia

In addition to its digestive and absorptive functions, the GIT also serves as a barrier to various microorganisms. Animal studies have shown that gut barrier dysfunction in obesity may lead to increased translocation of microbes or their products such as the lipopolysaccharide (LPS), which may lead to the so-called metabolic endotoxemia. The latter has been suggested as one of the possible mechanisms underlying the low-grade inflammation and insulin resistance in obesity and metabolic syndrome.[34,51] Besides, it has also been implicated in the development of atherosclerosis and nonalcoholic fatty liver disease.[52] LPS is a pro-inflammatory molecule derived from Gram-negative bacteria in the gut and its effects are mediated through TLR4. As described in the preceding sections, TLR4 stimulation activates adipose tissue macrophages and leads to inflammation and insulin resistance. Future research may uncover potential therapeutic targets along the LPS pathway, aid in the development of new treatment strategies and help us in tackling the obesity epidemic and its complications.

CONCLUSION

Genetic predisposition, dietary habits, an abundance of food and lack of physical activity each play a major role in the regulation of body weight. However, the pathogenesis of obesity involves mechanisms that extend far beyond these established drivers. Here, we have reviewed the emerging research in two key areas – the adipose tissue microenvironment and the gut microbiome – which are providing new insights into the pathogenesis of obesity. Only improved understanding of the complex physiology of body weight regulation and the development of obesity will inform preventive strategies and help us to broaden our therapeutic approaches.

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Conflicts of interest

There are no conflicts of interest.

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