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REVIEW

Key factors involved in obesity development

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Abstract Obesity has been considered to be a chronic disease that requires medical prevention and treatment. Intriguingly, many factors, including adipose tissue dysfunction, mitochondrial dysfunction, alterations in the muscle fiber phenotype and in the gut microbiota composition, have been identified to be involved in the development of obesity and its associated metabolic disorders (in particular type 2 diabetes mellitus). In this narrative review, we will discuss our current understanding of the relationships of these factors and obesity development, and provide a summary of potential treatments to manage obesity.
Level of Evidence Level V, narrative review.

Keywords Adipose tissue dysfunction · Gut microbiota · Mitochondrial dysfunction · Myofibers · Obesity · Type 2 diabetes mellitus

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Introduction

Obesity has reached epidemic proportions worldwide and is characterized by excessive or abnormal adiposity and chronic inflammation [1, 2]. Moreover, obesity is often related to the metabolic syndrome and is closely associated with major public health problems worldwide, such as type 2 diabetes mellitus (T2DM), cardiovascular disease, and cancer [3]. Therefore, obesity has been considered to be a chronic disease that requires medical prevention and treatment.

Intriguingly, many factors have been identified to be involved in the development of obesity and its associated metabolic disorders, such as adipose tissue dysfunction, alterations in myofiber types, mitochondrial dysfunction, changes in the gut bacterial composition, as well as others that are not listed in the present review have been associated with obesity development and contribute to this low-grade systemic inflammation, subsequently leading to insulin resistance and probably T2DM [4–8]. In this narrative review, we highlight current advances in understanding the roles of these factors in the development of obesity. Finally, we describe approaches to counteract obesity and related metabolic disorders.

Risk factors, obesity and T2DM

Obesity is a disease simply defined as a state of excessive and/or abnormal adiposity that may lead to T2DM. Obesity and T2DM are characterized by low-grade systemic

inflammation and insulin resistance in peripheral tissues [9]. Multiple factors, biologically, psychologically, or environmentally, contribute to the etiology of insulin resistance. Therefore, interest in better understanding the pathophysiological processes implicated in the manifestation of insulin resistance and obesity has increased dramatically, with the hope of identifying effective therapeutics and preventative strategies to conquer this disease state. In this regard, risk factors, including adipose tissue dysfunction, mitochondrial dysfunction, myofiber types, and gut microbiota have been reported to be associated with insulin resistance and obesity, and will be discussed first.

Adipose tissue: composition and function at a glance

Overweight and/or obesity continue to rise at an alarming rate worldwide, and adipose tissue plays a vital role in the regulation of energy homeostasis. In this context, interest in better understanding the composition and function of adipose tissue is rapidly rising in current medical research [10]. Adipose tissue is mainly composed of three types of fat, namely, white adipose tissue (WAT), brown adipose tissue (BAT), and the 'beige/brite' (brown in white) fat [11]. Notably, the primary cell type of adipose tissue is the adipocyte [12]. In response to overnutrition, WAT can expand its mass to store vast amounts of nutrients as triacylglycerol (TAG) or triglyceride molecules in unilocular white adipocytes in an effort to prevent lipid deposition and lipotoxicity in other metabolic tissues, such as the skeletal muscle and liver [13, 14]. Upon energy deficit, fat mobilization (lipolysis) occurs, favorably breaking down lipid stores (e.g., TAG) into its constituents, glycerol and non-esterified fatty acids (FAs), to target tissues [15]. Then, FAs enter downstream bioenergetics pathways, functioning as the intermediate acetyl-CoA, to resynthesize ATP as needed to meet the energy demand [16]. Upon systemic metabolic demand, the unparalleled capacity of adipose tissue for lipid storage and release links the cell biology of the adipose tissue physiology to whole-body metabolism [16]. Apart from its lipid-storing capacity, WAT is also a highly active endocrine organ, with the ability to synthesize and secrete numerous inflammatory molecules, allowing the crosstalk of adipose tissue with other tissues to mediate various physiological functions, such as insulin sensitivity, protein turnover, feeding behavior, and energy expenditure. The classical adipokines secreted by WAT are adiponectin, leptin, IL-6, and tumor necrosis factor (TNF-α) [17]. With regard to BAT, it can not only store nutrients as lipids, but also dissipate the chemical energy as heat in a process called nonshivering thermogenesis through uncoupling respiration [18]. Recent identification of BAT in human adults opens a new avenue to improve metabolic homeostasis [19–21]. Similarly to BAT, the 'beige/brite' fat can also dissipate their energy as heat (thermogenesis) [22]. Strategies aid in increasing this fat phenotype in WAT offers protection against obesity and T2DM [23]. Taken together, the functions of adipose tissue include adipogenesis, lipid metabolism, adipokine synthesis and/or secretion, and thermogenesis.

Adipose tissue dysfunction, obesity, and T2DM

The first organ influenced by excessive fat intake is the WAT, responding by higher fat deposition and consecutive hypertrophy and hyperplasia adipocytes [24]. In general, adipose tissue dysfunction is characterized by the inability of adipose tissue to store the surplus free FAs (FFAs) [25], decreased production of adiponectin, and increased production of inflammatory cytokines such as TNF-α, leptin and IL-6 [26]. In the context of obesity, adipose tissue is overloaded with triacylglycerol and cannot effectively store more lipids. Therefore, lipolysis increases, leading to increased FFAs levels in adipose tissue. The increased levels of FFAs can bind to macrophage toll-like receptor (TLR)-4 and can activate macrophage already present in adipose tissue, resulting in the activation of nuclear factor-κB and the production of proinflammatory cytokines such as TNF-α [27, 28]. TNF-α in turn activates adipocytes, further promoting lipolysis and elevating the expression of lots of genes [i.e., IL-6, macrophage chemoattractant protein-1 (MCP-1), and intracellular adhesion molecule-1 (ICAM-1)] [29–31]. MCP-1 and ICAM-1 further attract macrophages into adipose tissue [32]. As a result, the local paracrine loop between FFAs derived from adipose tissue and TNF-α derived from macrophages forms a gradual vicious cycle, potentially leading to a proinflammatory state of both adipocytes and macrophages [3]. This proinflammatory state further leads to disturbances in adipokine secretion, that is, a decreased secretion of adiponectin and an increased secretion inflammatory biomarkers, such as TNF-α and IL-6 [33, 34]. Thereafter, the altered adipokines' phenotype results in an increase in glucose production by the liver and a reduction in the glucose transporter 4 (GLUT4)-mediated glucose uptake by adipose tissue and muscles, accompanied by the inactivation of insulin receptor substrate-1 (IRS-1) and the attenuation of insulin signaling cascade [4]. In systemic insulin resistance, this attenuation or absence of the downstream effects of insulin signaling further promotes the lipolytic process in adipose tissue, leading to the ectopic lipid deposition in nonadipose tissues, contributing to systemic insulin resistance [16]. On the other hand, the surplus FFAs in adipose tissues can be released to nonadipose tissues such as the skeletal muscle and liver, resulting in ectopic lipid deposition if not utilized. The increased availability of FFAs induces the

oxidation of FFAs, producing an elevated concentration of citrate and acetyl-CoA that, respectively, inhibit phosphofructokinase and pyruvate dehydrogenase. Accordingly, the concentration of glucose-6-phosphate (G6P) increases and thus hexokinase is inhibited, finally leading to conditions related to insulin resistance such as impaired glucose uptake and glucose oxidation [35]. Therefore, ectopic lipid deposition is strongly associated with insulin resistance and then promotes the development of obesity-related metabolic diseases such as insulin resistance and T2DM [2]. Moreover, adipose tissue blood flow (ATBF) is reduced in obesity [36]. This impairment in ATBF may influence lipid handling in adipose tissue, thereby, further facilitating an elevated lipid supply to nonadipose tissues and contributing to ectopic fat deposition [37]. Subsequently, the increase in insulin resistance combined with insufficient secretion of beta cell insulin leads to T2DM [38]. Taken together, obesity is not just a weight control issue, but rather a disease state that is closely associated with adipose tissue dysfunction, characterized by the development of a low-grade systemic inflammation, leading to numerous chronic conditions associated with insulin resistance and T2DM.

Mitochondrial dysfunction, obesity and T2DM

The mitochondrion exerts crucial roles in the metabolism of FFAs to acetyl-coA for subsequent production of energy (NADH and ATP), energy expenditure, and disposal of reactive oxygen species (ROS) [39]. During differentiation of white adipocytes, the mitochondrion expands and increases FA β-oxidation [40–42]. Mitochondrial dysfunction is classically defined as the inability of mitochondria to produce and maintain sufficient levels of ATP, through oxidative phosphorylation, in response to energy demands [43]. In addition, mitochondrial dysfunction results from metabolic imbalance of energy input, energy production, and/or oxidative respiration. In particular, metabolic challenges such as increased FFAs and hyperglycemia consequent to excessive nutrient intake can increase the ROS production to evoke adipocyte mitochondrial dysfunction. As a consequence, compromised mitochondrial function reduces mitochondrial DNA (mtDNA) content, mitochondrial biogenesis, and the β-oxidation rate. As such, major adipocyte pathways are altered, leading to reduced adipogenesis, increased lipolysis, decreased FA esterification, and altered adiponectin levels; collectively, these alterations promotes changes in insulin sensitivity [44]. Defective or insufficient mitochondrial function is an established risk factor promoting insulin resistance and T2DM [45, 46]. There is an inverse relationship between the reduction in mitochondrial content (assessed by mitochondrial (mt) DNA) in WAT and insulin resistance in human subjects. The mtDNA directly associates with basal and insulin-stimulated lipogenesis; therefore, the dramatic reduction of mtDNA in adipose tissue may lower the adipocyte's lipid-storing capacity. [45, 47]. In addition, the mitochondrial dysfunction in the WAT may promote ectopic lipid accumulation in nonadipose tissues such as liver and muscle [45, 47], and may trigger the loss of homeostasis and elicit oxidative stress status. These alterations give rise to cell deterioration, insulin resistance, and/or to a greater lipid deposition in adipocytes [48, 49]. The increased adiposity mass and oxidative stress occurred in obesity can further elicit an inflammatory cascade, predisposing to obesity by stimulating the synthesis of the inflammatory cytokines such as TNF-α [4, 50]. Therefore, targeting factors that can promote mitochondrial function and the utilization of mitochondrial lipid, with less adverse effect, and can lower adiposity in animal models of obesity may have therapeutic benefits.

Myofibers, obesity, and T2DM

Skeletal fiber types vary in their structural, contractile, metabolic, and molecular properties, and thus, can be classified according to various parameters, including structural and contractile properties, metabolic enzyme profiles, and myofibrillar protein isoforms [8]. At present, the skeletal muscles in mammals mainly include type I fibers (slow-twitch, oxidative) and type II fibers (fast-twitch, glycolytic). Type I fibers are rich in mitochondrion and have high oxidative rates, while type IIb fibers display a reduced capacity to oxidize fat and to deal with oxidative stress. Moreover, type I fibers have a higher GLUT4 content and greater insulin-binding capacity than type II fibers [51, 52]. In this regard, type I fibers thus exert a vitally important role in mediating whole-body energy metabolism and insulin sensitivity [53]. Intriguingly, to adapt to different physiological requirements, the composition of muscle fiber types can change along the mammal's life after birth, a process called fiber type transformation [8].

Muscle fiber composition is at least in part predictive of obesity and diabetes. Generally, the proportion of type I fibers is lower than that of type II fibers in obese and diabetic subjects. The alterations in muscle fiber composition may result in mitochondrial dysfunction by elevating the glycolytic relative to the oxidative enzyme activities in muscle, thus reducing lipid oxidation and promoting adiposity [7, 54]. In addition, fiber type-specific differences can be found in the insulin signal transduction pathway. The proportion of type I fibers is positively associated with the insulin-induced glucose transport in skeletal muscle [55]. In support, previous studies have shown that in slow-twitch oxidative (soleus) muscle, tyrosine phosphorylation

of IRS-1 and IRS-1-associated PI3-kinase activity were markedly reduced in diabetic rats, compared with those of Wistar rats. In contrast, insulin signaling via IRS-1 was intact in fast-twitch glycolytic muscle [56]. Additionally, GLUT4 contribution from slow-twitch fibers was reduced to 77% in obese individuals, and further reduced to 61% in T2DM patients. It is speculated that the reduced GLUT4 contribution from the more insulin sensitive slow fibers may be primarily responsible for the defects in insulin-stimulated glucose uptake [57]. Conversely, increasing muscle oxidative fibers in morbidly obese women may result in a reduction in body mass, thus improving insulin action [58]; while increased glycolytic muscle mass may decrease whole-body insulin sensitivity [59]. Based on these data, we suggest a potential linkage between muscle fiber type, obesity and insulin resistance, and that a higher slow oxidative fiber phenotype is associated with increased insulin sensitivity leading to a decreased risk of developing diabetes.

Surprisingly, in contrast to the beneficial roles of type I fibers described above, several studies highlight the roles of type II fibers in preventing obesity and its associated metabolic disorders. For example, previous studies found that glucose tolerance was improved in parallel with increased mass of glycolytic muscle fibers, which was induced by blocking myostatin signaling through genetic or pharmacological treatment with soluble activin receptor type IIb [60, 61]. In agreement, fat mass loss and improved metabolic parameters were observed in obese mice, in which fast fibers were increased by constitutive activation of Akt [62]. These findings offer an intriguing new approach to understand the roles of myofibers in obesity and develop therapeutics to treat the emerging epidemics of obesity through interventions that preserve or restore glycolytic, fast-twitch myofibers.

In light of the abovementioned findings, it seems to be paradoxical concerning the role of myofibers in the modulation of obesity and metabolic dysfunction. Unfortunately, we do not have a plausible explanation for these paradoxical findings; further investigation into the role of myofibers is certainly warranted.

Gut microbiota and obesity

Apart from the abovementioned factors, disturbances in the gut homeostasis are also associated with the development of obesity and its related metabolic disorders. Body weight alteration and obesity can change the composition of the gut microbiota. The caecal microbiota of genetically obese hyperphagic *ob/ob* mice exhibited a proportional division-wide elevation of *Firmicutes* and an almost 50% reduction of *Bacteroidetes* relative to lean littermates independent of food consumption [63]. Similar results were observed in the fecal microbiota of lean versus obese human individuals, indicating lowered gut bacterial diversity [64, 65]. In diet-induced obese animals, a proportional elevation in *Firmicutes* and a similar reduction in *Bacteroidetes* was obtained, accompanied by a bloom of a single Mollicutes class within the *Firmicutes*, resulting in a marked reduction in overall diversity [66]. Within 24 h of diets alteration from a low-fat diet to an HFD, the marked alterations in the composition of gut microbiota occurred [67]. These alterations may influence energy storage and expenditure, causing a gain of body weight and an increase in host adiposity, thus predisposing the obesity and T2DM. Using germ free mice, obese animal models, and human subjects, previous studies found that despite consuming significantly less food, conventionally raised mice exhibited a 42% more increase of total body fat than germ free mice. When the "normal" gut microbiota from conventionally raised animals were transplanted into germ free recipients, germ free mice showed a 60% elevation in total body fat and adipocyte hypertrophy in spite of reduced food intake [68]. Consistent with these findings, other studies also showed that more total fat mass gain was obtained following the colonization of germ free recipients with gut microbiota from diet-induced obese mice than from lean donors [66].

One proposed mechanism by which shifts in gut microbiota composition could promote the development of obesity is via inflammation. A plethora of evidence has recently focused on disturbances in the gut homeostasis as a potential source of a low-grade systemic inflammation [6, 24]. More especially, alterations in the balance between different populations of gut bacteria will result in a disruption of the intestinal epithelium integrity that in turn lead to elevated passage of endotoxins [i.e., lipopolysaccharides (LPS)] into the circulation [6, 69, 70]. LPS is an endogenous ligand for specialized innate immune TLRs and can interact with the TLR4, leading to the activation of macrophages. Thereafter, activated inflammatory macrophages (M1 phenotype) may reach muscular and adipose tissues, fueling the peripheral inflammatory tone and eliciting a systemic low-grade inflammation [71]. However, disrupting LPS signaling confers protection against obesity and metabolic disorders [72]. Therefore, strategies aiming to mediate gut microbiota and/or to disrupt LPS signaling could contribute to attenuate the development of obesity and the occurrence of metabolic diseases.

Potential treatment options

Increasing factors have been identified and investigated involved in the treatment of obesity. These factors can be classified into four main types: (1) caloric restriction, (2) exercise, (3) pharmacological treatments, and (4) surgery. Some examples are discussed below.

Mounting evidence has demonstrated that caloric restriction is a widely accepted strategy to improve insulin sensitivity and to lower the incidence of diabetes in obese individuals [73, 74]. For example, 12 months of caloric restriction resulted in a mean reduction of 1.7 kg/m^2 in BMI [75]. Consistently, 16 weeks of caloric restriction in obese subjects at a high risk of developing T2DM led to an improvement in whole-body insulin sensitivity [76]. Moreover, the combination of caloric restriction and nutrition supplementation (such as leucine) is more effective in reducing the body fat than caloric restriction alone [77].

Another approach to tackling obesity and its associated disorders is increasing physical activity. Regular physical exercise is a successful therapeutic strategy for body weight maintenance and also for the prevention of obesity. For example, after 12 weeks of increased exercise and restricted caloric intake, the concentrations of proinflammatory cytokines (TNF-α, IL-6, and leptin) greatly decreased while anti-inflammatory cytokines (IL-10 and adiponectin) dramatically increased in obese people with metabolic risk factors [78]. In agreement, running reduced protein levels of the TLR4 and NF-κB pathways as well as proinflammatory markers in the hippocampus [79].

Apart from caloric restriction and exercise, the pharmacological treatment is also an important strategy for the prevention of obesity. For instance, in the long-term HFD (60% kcal from fat, lard-based) study, resveratrol had the ability to reduce peripheral markers of inflammation [76]. Recently, researchers highlight leucine, an essential and branched-chain amino acid, as a compound with potential therapeutic value towards obesity and its associated metabolic disorders [4]. Dietary leucine supplementation, either as part of a therapeutic regimen or alone, is effective to increase body weight loss, reduce WAT inflammation, improve lipid and glucose metabolism, and to enhance mitochondrial function. Interested readers can refer to [4] for further reading.

Finally, one of the last options to lower body weight and to improve metabolic disorders for obese subjects is surgery. Using two different surgeries [vertical sleeve gastrectomy and Roux-en-Y gastric bypass (ReY)], rats exhibited similar reductions in body weight. Moreover, the ReY procedure rescued obesity-altered spatial learning and memory functions [80].

Based on the abovementioned, increasing scientists are seeking ways to conquer obesity and metabolic disorders. However, there is currently no accepted "cure" for obesity. At present, it is commonly believed that the simple solution to obesity is weight loss. Nevertheless, weight loss is only the first phase of obesity management and may be meaningless and counterproductive without effective strategies to block weight regain [81, 82]. Therefore, the prevention of further weight gain should be given attention in future research. Moreover, obesity is a chronic and progressive condition and is associated with other chronic conditions (i.e., diabetes), preventing and treating obesity is, therefore, a lifelong event [82]. However, substantial barriers that can undermine long-term obesity management strategies exist, decreasing the long-term efficacy and effectiveness of obesity treatments. These barriers include time constraints, low socioeconomic status, and a wide range of comorbidities such as mental health, digestive, respiratory, and endocrine disorders [82]. Altogether, there is still a long way to go to completely conquer obesity and its associated metabolic disorders.

Concluding remarks and future perspectives

From the elements discussed above, it appears that obesity has a complex and multifactorial etiology. Many factors are closely associated with the development of obesity, and substantial barriers exist in the way to treat obesity. Thus, future studies will need to further address other unknown factors involved in obesity development and to develop novel therapies. In addition, understanding the relationship of these factors and obesity development may reveal novel sites for targeting drugs for the management of obesity and prevention of its associated metabolic disorders such as T2DM.

Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests

Ethical approval This article does not contain any studies with human participants performed by any of the authors.

Informed consent Informed consent was obtained from all individual participants included in the study.

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