RESEARCH PAPER

Inflammation and Metabolic Dysregulation: Links to Obesity and Type 2 Diabetes

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Abstract
Obesity has become a global epidemic, affecting approximately one-third of the world's population and serving as a primary risk factor for type 2 diabetes (T2D) and related metabolic disorders. This review examines the intricate relationship between obesity, inflammation, and insulin resistance, emphasizing the novel insights into immune cell interactions and their contributions to metabolic dysfunction that have not been thoroughly explored in prior reviews. We highlight white adipose tissue (WAT) as a crucial player in this process. Elevated body fat triggers a low-grade, chronic inflammatory response characterized by the recruitment and activation of pro-inflammatory macrophages, leading to the release of cytokines like TNF-α and IL-6, which disrupt insulin signaling and promote systemic inflammation. We comprehensively explore the role of macrophages as central players of inflammation within adipose tissue, particularly focusing on their phenotypic plasticity and impact on metabolic health. In addition, we discuss emerging therapeutic strategies targeting inflammatory pathways as potential interventions for managing obesity-related conditions. These include pharmacologic agents like salsalate, TNF-α inhibitors, IL-1β antagonists, and the anti-inflammatory properties of established diabetes medications such as thiazolidinediones and metformin. By elucidating the mechanisms underlying obesity-induced inflammation and its effects on glucose metabolism, this review aims to inform future research and clinical approaches to mitigate obesity and its associated metabolic complications.

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Introduction

Excess weight and fatness are the result of a persistent disturbance between energy consumption and expenditure, leading to the deposition of fat in adipose tissue (AT). About one-third of the global population suffers from excess weight or fatness, indicating that the prevalence of obesity has dramatically increased since 1980 [1,2]. Obesity is a complex condition influenced by genetic and lifestyle factors, leading to significant public health consequences. Improvements in lifestyle habits, such as increased physical activity and reduced caloric intake, are essential for weight management [3,4]. Effective glycemic control is achieved after gradual weight reduction of 10-16% from baseline, resulting in enhanced insulin sensitivity in AT, liver, and skeletal muscle [5-7].

Given this context, obesity is recognized as the most widespread endocrine disease globally and a major trigger for insulin resistance (IR) and diabetes mellitus [8-11]. According to the American Diabetes Association, diabetes mellitus is a cluster of diseases characterized by ineffective glucose metabolism. The incidence of diabetes mellitus has significantly increased over the past three decades, and it is now considered a leading cause of death worldwide. T2D is projected to affect more than 300 million individuals by 2025 as a sequela of obesity [12,13]. Persistent high glucose levels in T2D arise due to inadequate insulin production (β-cell dysfunction) and insulin resistance (failure of cells to respond to insulin). Understanding the interplay between obesity and IR will improve our insights into the etiology of T2D and guide more effective treatments for obesity-related conditions. Several studies have linked overeating to the activation of both innate and adaptive immune systems in tissues involved in energy balance regulation [14-16].

Initial evidence connecting inflammation to obesity and diabetes emerged from studies conducted in the early 1990s. These studies demonstrated that adipose tissue in obese rodents and humans exhibits inflammatory alterations and an increased release of pro-inflammatory molecules like TNF-α, which can lead to insulin resistance through the disruption of insulin signaling machinery [17-20]. The critical role of TNF-α is further supported by findings showing that blocking TNF-α in obese models enhances insulin sensitivity and glucose metabolism. Low-grade

chronic inflammation in adipose tissue, referred to as meta-inflammation, is strongly associated with excess body fat. This state is characterized by the persistence and activation of pro-inflammatory macrophages and other immune cells that secrete pro-inflammatory cytokines and chemokines [21-23].

Throughout obesity, not only does the macrophage count in adipose tissue increase, but their functional role also shifts from anti-inflammatory to pro-inflammatory. In individuals of normal weight, macrophages primarily exhibit anti-inflammatory properties [24]. In contrast, in obese individuals, these macrophages (designated as AT macrophages or ATMs) transition to a pro-inflammatory state, clustering around necrotic adipocytes and forming structures known as crown-like structures. This transition contributes to local and systemic inflammation and insulin resistance [25-27]. Despite ongoing research, the exact triggers of inflammation in obesity remain largely unexplained. However, morphological changes in adipose tissue, including adipocyte death, hypoxia, and mechanical stress, are known to initiate inflammatory processes. Given inflammation's critical role in T2D and related metabolic complications, there is increasing interest in targeting inflammatory pathways to impede disease progression [28,29]. This review focuses on elucidating how the loss of immune regulation contributes to disease development in adipose tissue, emphasizing both cellular and molecular mechanisms driving inflammation.

Search Strategy

In the search strategy for this review, multiple databases were utilized to gather relevant literature. PubMed was accessed for peer-reviewed articles specifically focusing on obesity, inflammation, insulin resistance, and associated metabolic disorders. Web of Science provided multidisciplinary research articles and citations that are relevant to the examination of these topics. Scopus was included for its comprehensive abstracts and citation analysis within the health and life sciences. The Cochrane Library was consulted to find systematic reviews related to the therapeutic interventions discussed in the review. Google Scholar was also employed to facilitate broad searches across various academic disciplines, capturing grey literature that might not be indexed in traditional databases.

Various keywords and phrases were used in different combinations during the search, including terms like "Obesity," "Inflammation," "Insulin Resistance," "Type 2 Diabetes," "White Adipose Tissue," "Cytokines," "Macrophages," "Adipokines," as well as therapeutic agents such as "Metformin," "Salsalate," "TNF-α inhibitors," "IL-1β antagonists," and "Thiazolidinediones."

The inclusion criteria for selecting studies were specifically defined. Only studies published in English from 1990 to 2023 were considered, and these included peer-reviewed articles such as randomized controlled trials, observational studies, and systematic reviews. The research had to focus on the mechanisms that link obesity with inflammation and insulin resistance, as well as therapeutic strategies aimed at targeting inflammation in the context of obesity-related metabolic disorders. Excluded from the review were articles not published in English, studies centering solely on pediatric populations unless they had relevance to adult obesity and metabolism, non-peer-reviewed content such as opinion pieces and editorials, and any studies that did not directly address the relationships between obesity, inflammation, and insulin resistance.

The selection process involved several steps. Initially, two independent reviewers conducted a preliminary screening of all retrieved articles based on their titles and abstracts. Articles deemed irrelevant or failing to meet the inclusion/exclusion criteria were removed from consideration. Those that passed this initial screening underwent a full-text review, where the articles were examined in detail. Any disagreements that arose between reviewers during this process were resolved through discussion or consultation with a third reviewer. The final selection of studies was systematically recorded, and detailed reasons for the exclusion of particular articles were documented to ensure transparency.

For data extraction and analysis, a standardized data extraction form was created to capture essential information from the selected studies. This included data on authorship, publication year, study design, population characteristics, details of interventions, outcome measures, and key findings. The quality of the included studies was assessed using appropriate tools, such as the Cochrane risk-of-bias tool for randomized controlled trials and the Newcastle-Ottawa Scale for observational studies. The results of the quality assessment were integrated into the review to provide contextual information about the findings.

The synthesis of findings from the selected studies was conducted narratively, highlighting key themes—particularly the role of inflammation in mediating insulin resistance in obesity. When applicable, meta-analytic techniques were employed to quantify the effects of specific interventions on insulin resistance, provided there was sufficient homogeneity among the studies included.

By employing this rigorous search and selection strategy, the review aims to provide a comprehensive understanding of the intricate relationships between obesity, inflammation, and insulin resistance, as well as to explore the therapeutic options available for intervention.

The Inflammatory Phenotype of White Adipose Tissue

White adipose tissue (WAT) primarily serves as a fat reservoir and acts as a major endocrine organ, releasing signaling molecules collectively termed adipokines and cytokines into circulation. These compounds play key roles in regulating various metabolic processes, including insulin sensitivity, glucose uptake, and fatty acid metabolism. Cytokines play a crucial role in modulating inflammation while supporting tissue repair and vascularization [30,31]. When an individual gains weight and becomes obese, WAT undergoes significant changes, including the

emergence of inflamed, dysfunctional adipocytes and infiltration of immune cells into the tissue. These inflamed adipocytes release pro-inflammatory cytokines that negatively impact normal WAT function and other organs [32,33]. In this context, WAT can be perceived as both an immune and secretory organ, positioning obesity as a condition rooted in chronic inflammatory processes [34,35].

Research involving both animal models and human populations has consistently shown a direct correlation between excess caloric intake, adipose tissue inflammation, and metabolic dysfunction. A study by Lee et al. demonstrated that inflammation is pivotal in the development of insulin resistance induced by a long-term Western-style diet in immunocompromised mice. An important feature of inflammation in expanding WAT is its persistent, low-grade nature, which is resistant to resolution and is often referred to as "metaflammation" [36-38]. Inflammation generally incurs an energy cost by increasing energy expenditure and reducing energy consumption through direct and indirect pathways. Pro-inflammatory cytokines such as TNF-α, IL-1, and IL-6 augment energy expenditure by acting on central and peripheral metabolism [39-41].

Production of leptin, an important adipokine, rises in response to inflammation, triggered by hypoxia and inflammatory stimuli. Furthermore, TNF-α enhances leptin receptor expression, reinforcing leptin's role in boosting energy expenditure and suppressing appetite [42-45]. However, intriguingly, inflammation in adipose tissue resulting from overnutrition does not lead to a notable increase in overall energy expenditure, allowing for the coexistence of inflammation and weight gain in obesity. Despite this, the inflammatory response in adipose tissue resembles traditional inflammation, characterized by immune cell infiltration from the bone marrow and cytokine release by both adipocytes and resident immune cells. Even in individuals with normal weight, inflammatory adipose tissue can trigger systemic inflammation via cytokine release [46,47]. WAT exhibits diverse inflammatory profiles due to its anatomical position and structural features. Studies show that obesity leads to a more pronounced inflammatory response in visceral WAT (VAT) compared to subcutaneous WAT (SAT). VAT in obese individuals contains a greater density of macrophages and exhibits increased adipocyte hypertrophy compared to SAT [48-50]. Additionally, inflammation in VAT correlates with impaired lipogenic marker expression, suggesting that more cells assume an inflammatory role over lipid storage, contributing to metabolic dysfunction, including ectopic fat accumulation in the liver and muscle. Given its direct effects on insulin regulation, inflammation in VAT significantly impacts obesity-related conditions, including insulin resistance and T2D [51,52].

Research demonstrates that both VAT and SAT contribute to inflammation but play distinct roles in metabolic dysregulation (see Table 1). Studies involving animal models suggest that the relative impact of VAT and SAT on metabolism can be illustrated through surgical fat transplantation experiments [53]. To explore the distinct metabolic influences of VAT and SAT, Rytka et al. transplanted epididymal VAT into areas draining the caval or portal systems. The procedure induced inflammatory responses in both groups, but only those with mesenteric transplants exhibited marked increases in IL-6 and free fatty acids (FFA) in the portal vein, ultimately leading to impaired glucose tolerance. Human studies further validate the differential metabolic impact of VAT and SAT [54,55]. For an equivalent quantity of AT, VAT absorbs more meal-derived FFA compared to SAT in both men and women; notably, omental fat (a VAT subtype) exhibits heightened FFA absorption from plasma compared to abdominal SAT in women. These findings underscore the anatomical and structural advantages of VAT in influencing endocrine organs like the liver, which are pivotal to insulin and metabolic regulation [56,57].

Table 1. Impact of Adipose Tissue Types on Inflammation and Metabolism

Adipose Tissue Type	Key Characteristics	Effects on Metabolism
Visceral Adipose Tissue (VAT)	Greater density of macrophages; increased hypertrophy in obese individuals.	More pronounced inflammatory response; correlates with insulin resistance.
Subcutaneous Adipose Tissue (SAT)	Exhibits a less intense inflammatory profile compared to VAT.	Less influential in systemic inflammation compared to VAT.
Transplantation Studies	VAT and SAT play distinct roles in metabolism; VAT has a greater absorptive capacity for FFA.	Hirnse et al.'s transplantation experiments showed metabolic discrepancies.

The Role of Inflammation and Macrophages

In obesity, expanded adipose tissue produces elevated levels of pro-inflammatory cytokines that activate both the IKKβ/NFκB and JNK pathways, leading to insulin resistance in both adipose and liver tissues. The inflammatory response in adipose tissue is a key factor

in obesity-related insulin resistance, with various immune cell subtypes contributing to the regulation of inflammation. While adipocytes are essential for modulating inflammation and tissue remodeling via cytokine secretion and antigen presentation, macrophages play a central role in inflammation and metabolic dysfunction [58-60]. Macrophages are immune cells found in adipose tissue (AT) and exhibit diverse roles, such as phagocytosis of dead cells, remodeling of the extracellular matrix, regulation of blood vessel formation, and maintenance of homeostasis within AT. In obesity, there is a notable increase in monocyte and macrophage recruitment to AT. In lean human visceral AT, macrophages constitute approximately 10% of the stromal vascular fraction; this proportion can escalate to roughly 40% in the setting of obesity [61-63].

The concept of "phenotypic switching" of macrophages in adipose tissue has emerged, wherein macrophages transition from an anti-inflammatory state (M2 macrophages) to a pro-inflammatory state (M1 macrophages). M2 macrophages, typically induced by Th2 cytokines such as IL-4, IL-10, and IL-13, are prevalent in lean AT and contribute to normal adipocyte function through tissue repair and angiogenesis [64-66]. In contrast, M1 macrophages become predominant in obesity, activated by signals like lipopolysaccharide (LPS) and Th1 cytokine IFN-γ, producing pro-inflammatory factors such as TNF-α and IL-6, thereby exacerbating insulin resistance. While the "phenotypic switching" model initially provided valuable insights, evolving research suggests that macrophages exhibit significant adaptability, and their phenotypes may not fit neatly into M1 or M2 categories, instead existing along a spectrum of activation states [67-69]. We schematically depicted the concept of "phenotypic switching" of macrophages in Figure 1.

Recent insights posit that these metabolic activation states, termed "MMe," are influenced by metabolic stimuli, including elevated levels of free fatty acids, insulin, and glucose. Proteomic analyses have established that MMe macrophages express unique surface markers (e.g., ABCA1, CD36, and PLIN2) essential for lipid metabolism, indicating their role in lipid handling and inflammation regulation [70-78]. The infiltration of macrophages into expanding adipose tissue potentially plays a critical role in initiating inflammation and driving insulin resistance during obesity. These macrophages may foster an environment conducive to the negative metabolic effects associated with expanding AT. Yet, some studies suggest that inflammation in adipose tissue could arise as a consequence of insulin resistance, rather than being the primary causative factor, underscoring the complexity of these interrelationships in obesity [79,80].

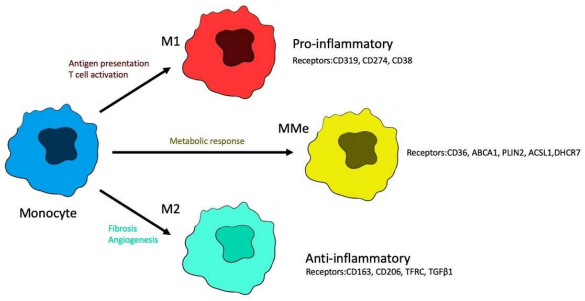

Figure 1. Macrophage phenotypic switch. Based on [72-74].

Inflammation as a Therapeutic Target for Metabolic Diseases

Chronic inflammation, especially in adipose tissue (AT), is now recognized as a key factor in the development of type 2 diabetes (T2D) and its related complications. The link between obesity, AT inflammation, and metabolic diseases has made targeting inflammatory pathways an attractive strategy for treating these conditions [5,21]. Inflammation is seen as a central cause of these common health issues. Although a few anti-inflammatory treatments have been tested in obese individuals with insulin resistance (IR), more clinical trials are needed to confirm their effectiveness. The number of drugs available that target various parts of the immune system and improve different aspects of metabolism is growing rapidly [81-83].

Therapeutic approaches to targeting inflammation in insulin resistance (IR) and type 2 diabetes (T2D) can be categorized based on their mechanism of action into two main groups: (i) pharmacologic approaches that directly target inflammation, and (ii) diabetes drugs that also possess anti-inflammatory properties [84-86]. In Table 2, we summarized key features of various therapeutic strategies.

Table 2. Therapeutic Strategies Targeting Inflammation in Obesity

Therapeutic Approach	**Mechanism of Action**	**Clinical Evidence**
Salsalate	Inhibits NF-κB pathway	Improves insulin sensitivity; lowers HbA1c in T2D
TNF-α Inhibitors	Neutralizes TNF-α	Mixed results in T2D; lowers fasting glucose in non-T2D
IL-1β Antagonists	Blocks IL-1 receptor	Improved blood sugar control; beneficial in RA + T2D

Therapeutic Approach	Mechanism of Action	Clinical Evidence
Thiazolidinediones (TZDs)	PPARγ agonists, anti-inflammatory effects	Reduces AT macrophages, enhances insulin sensitivity
Metformin	Reduces liver glucose production, inhibits inflammatory cytokines	Lowers CRP levels; improves metabolic outcomes

Therapeutic approaches

Salsalate

Salsalate is a salicylate derivative that belongs to the non-steroidal anti-inflammatory drug (NSAID) class. Research indicates that salsalate can be effective in improving glycemic control among individuals with type 2 diabetes (T2D). The mechanism by which salsalate mitigates hyperglycemia involves the inhibition of the NF-κB signaling pathway, a cornerstone finding established by Shoelson et al. in 2001 [87,88].

Goldfine expanded on initial findings by conducting clinical studies demonstrating that salsalate could reduce fasting glucose and triglyceride levels, increase adiponectin concentrations, improve glucose utilization during hyperinsulinemic-euglycemic clamps, and enhance insulin clearance among diabetic patients. These results were corroborated in multiple interdisciplinary, randomized, placebo-controlled trials involving T2D patients [89]. The first trial observed a significant improvement in insulin sensitivity and a reduction in HbA1c levels by 0.5% compared to a placebo group over 14 weeks. A second 48-week study, including 283 participants (146 receiving salsalate and 137 receiving the placebo), revealed a smaller yet significant reduction in HbA1c levels (–0.33%) and serum triglycerides with salsalate treatment. Additionally, treatment with salsalate correlated with diminished levels of glycation end products [87-89]. Emerging evidence suggests that the metabolic benefits of salsalate are likely mediated via AMPK activation. While the overall effects on glycemic control are modest, salsalate's affordability and favorable safety profile make it a viable option for managing T2D [90,91].

TNF-α Inhibitors

In 1993, a preclinical study demonstrated the role of TNF-α in the development of insulin resistance in adipose tissue. This led to the hypothesis that blocking TNF-α could have therapeutic benefits [92]. However, clinical study results have been disappointing. Although TNF-α neutralizing antibodies are effective for treating many other inflammatory diseases and have shown slight improvements in blood sugar control in some patients, results in patients with type 2 diabetes (T2D) have been inconclusive [93,94]. Despite promising effects in mice, a human clinical trial found that anti-TNF-α therapy did not improve insulin sensitivity in T2D patients. On the other hand, a study of obese individuals without T2D showed that inhibiting TNF-α for 6 months could lower fasting glucose and increase adiponectin levels [95,96].

IL-1β Antagonists

IL-1β plays a critical role in orchestrating obesity-related inflammation and contributes to the pathophysiology of type 2 diabetes (T2D) through its adverse impact on pancreatic β-cells under hyperglycemic conditions. A proof-of-concept study investigating IL-1 receptor (IL-1R) blockade in T2D patients over 13 weeks showed significant improvements in blood sugar control, β-cell function, and a reduction in systemic inflammation markers [97,98]. A subsequent follow-up demonstrated that even 39 weeks post-treatment, β-cell insulin secretion remained elevated, and C-reactive protein (CRP) levels were significantly reduced. The long-lasting effects of IL-1R antagonism likely stem from the inhibition of IL-1β's self-reinforcing loop. Further studies have supported the potential of IL-1β blockade, revealing significant reductions in HbA1c in treated T2D patients [99].

Pathological IL-1β activation is implicated in various comorbidities associated with T2D, including Crohn's disease, gout, and rheumatoid arthritis (RA). A multicenter randomized controlled trial specifically assessed the effects of IL-1R antagonism on blood sugar control in RA patients with concurrent T2D over a 6-month period [100,101]. Thirty-nine participants were randomized to receive either anakinra (an IL-1R antagonist) or TNF inhibitors to compare therapeutic outcomes in T2D. After 3 and 6 months of treatment, anakinra led to markedly improved metabolic outcomes, with HbA1c reductions exceeding 1%, a notable deviation from TNF inhibitors, which had no significant impact. Both treatment arms exhibited gradual declines in RA severity, underscoring the potential of IL-1 inhibition to effectively target both conditions and improve participant outcomes. The pronounced HbA1c reduction may reflect more severe pathogenic mechanisms inherent to T2D in the context of RA, suggesting the potential of a common pathogenic pathway suitable for dual-targeted therapeutic strategies [102,103].

Thiazolidinediones

Thiazolidinediones (TZDs) are antidiabetic drugs that enhance insulin sensitivity and improve blood sugar levels by acting as agonists for the PPARγ nuclear receptor. In addition to their metabolic effects, TZDs also possess anti-inflammatory properties; they inhibit NF-κB activity and decrease the expression of genes regulated by NF-κB [104,105].

Inhibiting the NF-κB pathway decreases the content of adipose tissue macrophages (ATMs), helps to restore the anti-inflammatory M2 macrophage phenotype, and promotes the recruitment of anti-inflammatory regulatory T cells in adipose tissue [106-108].

Moreover, the ability of TZDs to lower circulating inflammatory mediators like CRP and MCP-1 appears to be independent of their effects on glycemic control. Therefore, TZDs likely operate through multiple mechanisms, and their anti-inflammatory properties are not yet fully understood [109,110].

Metformin

The precise mechanism of metformin's action remains partially characterized, yet it is known to decrease hepatic glucose production and enhance glucose utilization in peripheral tissues. In addition to its established metabolic effects, metformin exhibits anti-inflammatory capabilities, which are shown to directly reduce reactive oxygen species production and suppress multiple pro-inflammatory cytokines. Emerging evidence further indicates metformin's immune-modulatory effects [111-113]. Extensive literature has reviewed metformin's influence on diverse immune cell types, including T cells, B cells, monocytes/macrophages, and neutrophils, all of which contribute to autoimmune and inflammatory diseases. Within these immune cells, metformin transiently inhibits complex I of the mitochondrial electron transport chain, resulting in elevated AMP/ATP ratios. This decrease in ATP triggers AMPK activation, leading to mTOR inhibition—which is integral to cellular processes, such as metabolism, cytokine production, antigen presentation, and macrophage functioning [114-116].

Moreover, metformin impacts multiple signaling pathways related to immune cells, such as NF-κB and JNK. It has been shown to inhibit TNF-α-induced activation of the NF-κB pathway, thereby reducing IL-6 production through PI3K-dependent AMPK phosphorylation. Notably, metformin can diminish IL-1β production in lipopolysaccharide-stimulated macrophages in a dose-dependent manner, an effect occurring independently of AMPK activation [117,118]. Metformin is also effective in lowering inflammatory markers like CRP in patients with impaired glucose tolerance and T2D. Interestingly, the anti-inflammatory effects of metformin resemble those of TZDs, suggesting potential shared mechanisms that are independent of glycemic control. In animal models, targeting inflammatory pathways has shown promise in enhancing insulin resistance linked to obesity. However, continuous clinical investigations are paramount to affirming metformin's therapeutic relevance in humans. This is vital for establishing the translational applicability of identified mechanisms [119,120].

As type 2 diabetes (T2D) is a heterogeneous disorder, the lack of clinical biomarkers indicative of anti-inflammatory effects within adipose tissue complicates comparative analyses of therapeutic efficacy. Profiling these biomarkers in T2D patients is essential for identifying individuals who would benefit most from anti-inflammatory interventions [121,122].

Conclusion

In conclusion, the rising prevalence of obesity globally is intricately linked to the emergence of insulin resistance and type 2 diabetes, with chronic inflammation in adipose tissue serving as a central mechanism in this connection. The shift in macrophage populations within WAT from anti-inflammatory to pro-inflammatory states exacerbates metabolic dysregulation, highlighting the critical role of immune dysregulation in obesity's pathology. Addressing these inflammatory processes opens new avenues for therapeutic intervention, and innovative strategies aimed at targeting specific inflammatory pathways alongside existing antidiabetic medications hold promise for improving metabolic outcomes among obese individuals.

Future research should focus on elucidating the complex interrelations between immune responses and metabolic health while identifying biomarkers predictive of responses to anti-inflammatory therapies. By advancing our comprehension of these factors, we can strive to develop more effective treatments to counter obesity and its myriad health consequences.

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