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Influence of Weight Loss and Weight Regain on Adipose Tissue Inflammation

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ABSTRACT: The global rise in obesity underscores the urgent need for effective long-term weight-management strategies. Weight loss (WL) is extremely beneficial in combating obesity complications, justifying the great success of recent WL medications. However, most individuals trying to lose weight will fail to maintain a lower body weight. Weight regain following WL increases the risk of cardiovascular disease and mortality. Adipose tissue inflammation is a critical mediator of metabolic dysfunction in obesity, contributing to cardiovascular complications. In obesity, chronic low-grade inflammation, marked by immune infiltration and dysregulated adipocyte function, contributes to systemic insulin resistance and metabolic comorbidities. However, the adipose tissue response to WL and subsequent weight regain is distinct from that in non–weight-fluctuating obesity and far less studied. This review synthesizes current literature to elucidate the dynamic shifts in adipose tissue across the continuum of obesity, WL, and weight regain.

Key Words: cardiovascular diseases ■ cytokines ■ endothelial cells ■ insulin resistance ■ lipogenesis

The global prevalence of obesity has risen dramatically over the past few decades. Obesity drives the development of several complications such as insulin resistance, type 2 diabetes, and cardiovascular disease.[1]

Weight loss (WL) is the preferred strategy against obesity because it reduces many of its associated complications. Weight-management interventions include lifestyle changes, pharmacotherapy such as glucagon-like peptide-1 receptor agonists (eg, semaglutide and tirzepatide), or bariatric surgery. The magnitude and benefits of WL vary depending on the initial grade of obesity, as well as the intervention applied, but overall studies have reported significant improvements in obesity complications and quality of life.[2] Therefore, maintaining WL is the goal for management of obesity comorbidities. However, weight regain (WR) after WL is common due to complex physiological, behavioral, and environmental factors. Metabolic adaptations, such as a decline in resting energy expenditure and increased hunger hormones, as well as gradual return to previous eating and activity patterns, promote WR.[3,4]

An added layer of complexity to fully understanding metabolic disease lies in the dynamic nature of physiological metabolism. Fluctuation of body weight, broadly known as weight cycling, has been linked to adverse metabolic dysfunction, heightening the risk of cardiovascular disease and diabetes, and increased risk for mortality in humans.[5–10] Although intentional WL can improve cardiometabolic parameters (blood pressure, lipid profiles, and glycemic control), regaining the lost weight often negates these benefits or even exacerbates these conditions.[4,9,10] WR may intensify chronic low-grade inflammation by promoting cyclical expansion and contraction of adipose depots.[11] This repeated adipose tissue remodeling, together with fluctuations in other cardiometabolic factors, can strain the vasculature, contribute to endothelial dysfunction, and impair insulin secretion- all of which are core risk factors for cardiovascular disease.[12,13]

The adverse effects of obesity on inflammation and subsequent disease are not yet fully understood.

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Nonstandard Abbreviations and Acronyms

ATM	adipose tissue macrophage
BAT	brown adipose tissue
FFA	free fatty acid
HIF-1α	hypoxia-inducible factor-1α
IFN	interferon
IL	interleukin
LAM	lipid-associated macrophage
MCP-1	monocyte chemoattractant protein-1
TNF-α	tumor necrosis factor-α
Treg	regulatory T cell
VAT	visceral adipose tissue
WAT	white adipose tissue
WL	weight loss
WR	weight regain

Highlights

- Weight loss reverses many detrimental features of obese adipose tissue but incompletely restores tissue homeostasis.
- Weight regain reactivates and often exacerbates inflammatory pathways, driving worsened metabolic dysfunction compared with primary obesity.
- Obesity imprints long-lasting reprogramming in several adipose tissue cell types that persists after weight loss and accelerates inflammation during weight regain.
- Preventing chronic weight cycling requires sustainable weight-management strategies and therapies targeting persistent adipose-immune dysfunction.

Importantly, our understanding of the processes and consequences of WL and WR is far less complete than in non–weight-fluctuating (primary) obesity. Because many reviews addressed the influence of obesity on adipose remodeling, in this review, we focus on the regulation of adipose tissue inflammation during WL and WR.

ADIPOSE TISSUE TYPES AND FUNCTION

Adipose tissue is composed of 2 major types: white adipose tissue (WAT) and brown adipose tissue (BAT). WAT is responsible for energy storage in the form of triglycerides and the release of free fatty acids (FFAs) during periods of energy deficit. Conversely, BAT uses its stored energy to fuel heat production to maintain core body temperature. A third category, beige adipocytes, can emerge within WAT depots under certain stimuli (eg, cold exposure) and function similarly to BAT.[14] While BAT is a critical adipose depot regulating whole-body metabolism,[15] studies exploring the effects of WL and WR on BAT are lacking, and therefore, this review will focus on WAT.

In lean individuals, WAT depots are metabolically flexible and exhibit a healthy balance of adipogenesis, lipogenesis, and lipolysis. Adipose tissue also serves as an endocrine organ, secreting adipokines, lipids, cytokines, and growth factors that regulate appetite, insulin sensitivity, and energy homeostasis.[16] Many cell types reside in WAT, including adipocytes, preadipocytes, endothelial cells, fibroblasts, and immune cells. Importantly, visceral adipose tissue (VAT), located in the abdominal cavity, is more prone to inflammation and insulin resistance than subcutaneous adipose tissue, which is often more benign and even protective.[14]

New transcriptomics methodologies have revolutionized our understanding of adipose tissue by providing unprecedented resolution of its cellular heterogeneity.[17–19] While earlier work has suggested that there are multiple types of white adipocytes, single-nucleus RNA-sequencing allows for finer characterization of adipocyte subpopulations and their selectivity for variables such as adipose depot and metabolic state.[20] Initial comparisons between mouse and human find that while there are many overall cross-species similarities in adipocytes, they do not cluster into the same subpopulations. These differences could be due to experimental conditions, limitations in mapping subpopulations across species, or simply species differences in adipocyte function, which will require elucidation in future studies.

ADIPOSE TISSUE REMODELING

Primary Obesity

With the development of obesity, WAT undergoes extensive remodeling. Excess nutrient intake leads to chronic positive energy balance, causing WAT to expand either through increased adipocyte size (hypertrophy) or number (hyperplasia). Lean WAT expansion often prioritizes hyperplasia, generating smaller adipocytes. In obesity, however, WAT expansion is often dominated by hypertrophy. While early studies showed reduced insulin sensitivity in large compared with small adipocytes,[21–23] these findings have not been recently validated,[24] and the underlying mechanisms that could explain this relationship remain unexplored. Nonetheless, as adipocytes enlarge, local hypoxia may ensue due to inadequate angiogenesis and insufficient oxygen delivery. This hypoxic stress triggers the stabilization of HIF-1α (hypoxia-inducible factor-1α) and promotes cytokine release (eg, MCP-1 [monocyte chemoattractant protein-1] and IL [interleukin]-6), extracellular matrix deposition, fibrosis, and cell death.[26] In turn, dying adipocytes release damage-associated molecular patterns that recruit immune cells, especially macrophages, to clear cellular debris. This self-perpetuating cycle drives a proinflammatory state in WAT.[16]

Weight Loss

WL reverses many of the detrimental alterations in obese WAT by remodeling adipocyte and stromal populations, reducing senescence and hypertrophy, and partially restoring lean-like gene programs.[27–29] Reduced energy intake creates a negative energy balance, leading to mobilization of FFAs from adipocytes to the circulation through lipolysis, and generally changes the types of lipids secreted from WAT. For instance, increased secretion of bioactive sphingolipids from WAT correlates with inflammation and insulin resistance in obesity,[30] while WL induces dynamic changes in adipose and plasma lipids, which have been suggested to favor weight maintenance.[31,32] WL-induced lipid secretion decreases adipocyte size and reduces adipocyte number in some contexts.[33–35] This shrinking of adipocytes correlates with improved insulin sensitivity, enhances mitochondrial oxidative phosphorylation, and normalizes adipokine secretion, including increased production of protective adipokines like adiponectin.[36–43] Interestingly, early WL is marked by macrophage recruitment to WAT, possibly to deal with the increased FFA released from adipocytes, which subsides with extension of the WL period.[44] However, how WL influences adipose landscape and function over time is largely unknown. Furthermore, as adipocytes shrink, hypoxia is alleviated due to improved oxygen diffusion and potentially increased angiogenesis.[40] The reversal of the proinflammatory milieu (eg, immune cell infiltration, abnormal adipokine, and cytokine secretion) also contributes to improved metabolic health.[45–48] The mechanisms by which WL reverses, and not just halts, much of the damage caused in WAT by obesity are largely unknown. Moreover, while WL is beneficial, some of the abnormalities induced by obesity do not resolve, including immune cell exhaustion, adipose tissue fibrosis, and epigenetic modifications sustaining inflammatory gene upregulation and adipocyte dysfunction,[49–51] with underlying mechanisms undetermined.

Weight Regain

WR often initiates a rapid resurgence of the detrimental adipose tissue changes observed in obesity, sometimes even exceeding its initial severity. This process involves hypertrophy rather than promoting hyperplasia.[22,37,38] Hypertrophy can lead to a swift return of adipocyte dysfunction, including decreased insulin sensitivity and altered adipokine secretion.[13,39] Studies on mouse models of obesity revealed a substantial increase in adiposity upon WR correlating with circulating leptin but not adiponectin levels.[39,40] Moreover, VAT experiences a rapid resurgence of inflammation and cell death, exacerbating the secretion of proinflammatory cytokines such as TNF-α (tumor necrosis factor-α) and IL-6.[56]

IMMUNE CELL DYNAMICS ACROSS DIFFERENT METABOLIC CONDITIONS

Primary Obesity

Adipose tissue macrophages (ATMs) are the most extensively studied immune cells in WAT. Macrophage depletion results in enhanced lipolysis[44] and improved glucose and insulin tolerance in both obese and lean mice, while increasing adiponectin and decreasing leptin plasma levels,[57] underscoring the relevance of this cell type in the metabolic control under obese conditions.

Newer findings acknowledge the existence of ATM phenotypic, functional, and spatial heterogeneity in different metabolic conditions.[58,59] In the lean state, ATMs are mostly resident cells of embryonic origin.[60] Resident ATMs are typically located near the vasculature (perivascular macrophages)[61] and sympathetic nerves (nerve-associated macrophages).[62,63] In general, resident ATMs in the lean state help maintain tissue homeostasis by clearing debris and promoting remodeling, lipid recycling, and supporting insulin sensitivity.[64] In obesity, both the number and phenotype of ATMs change dramatically, initially because of resident macrophage proliferation, followed by infiltration of bone marrow–derived monocytes that differentiate into macrophages and expand locally.[65] ATMs manage the adipocyte lipid load through several mechanisms, including uptake, storage, and hydrolysis of lipids from adipocyte-derived exosomes.[66] Furthermore, ATMs participate in dead adipocyte clearance by secretion of lysosomal content into dying adipocytes (exophagy)[67] in a process regulated by NOX2.[68]

The term lipid-associated macrophages (LAMs) has been adopted to describe a population of $CD11c^+/CD9^+/TREM2^+$ cells that accumulate surrounding dying adipocytes forming crown-like structures, a histological hallmark of inflamed WAT.[59,69] LAMs are distinguishable from other ATMs by their lipid-handling gene signature, including lipid/lipoprotein transporters (*Trem2*, *Cd36*, *Fabp4*, and *Fabp5*) and lipases (*Lipa* and *Lpl*).[59] Accordingly, LAMs exhibit specialized functions that support their role in the obese tissue milieu, including FFA uptake via CD36[59] and possibly TREM2-driven efferocytosis through phospholipid recognition on apoptotic cells, as shown in the brain and liver.[70,71] Altogether, this evidence highlights the role of macrophages in sustaining protective lipid-buffering in obesity.[59,72–75]

In lean adipose tissue, regulatory T cells (Tregs) and T-helper type 2 cells predominate, producing anti-inflammatory cytokines (eg, IL-10) that help maintain metabolic homeostasis.[76] Remarkably, Tregs disappear in the obese VAT, with recent findings suggesting that IFN (interferon)-α[77] and loss of IL-27[78] signaling, as well as disturbed cholesterol homeostasis,[79] prevent Treg maintenance in mice, while IFN-γ mediates these changes in humans.[80] Obesity causes a shift toward

a proinflammatory T-cell milieu, characterized by an increase in CD8+ T cells capable of promoting macrophage recruitment and Th1 cells producing IFN-γ, which contributes to proinflammatory macrophage polarization and insulin resistance.[81] Recently, a role for γδT cells has been established, which maintain adipose Tregs and thermogenesis via production of IL-17.[82,83]

B cells contribute to adipose tissue function through the production of pathogenic antibodies that can recognize the ectodomain of the insulin receptor,[84] secretion of reparative antibodies that promote dead adipocyte clearance, and improved insulin resistance[85] by modulating T-cell responses.[86] In addition, adipose-resident B1-B cells secrete protective IgM antibodies, which have been associated with improved metabolic parameters in obese humans.[87] On the other hand, B2 cells are recruited and activated in the WAT following leukotriene B4 receptor signaling, releasing IL-1β and IL-6, and contributing to worsened glucose and insulin sensitivity in coordination with T cells and macrophages.[88] A detailed account of these and other immune cell functions in obese WAT is reviewed elsewhere.[64]

Weight Loss

The immune response in the context of WL is dynamic, and the outcome in terms of cell abundances and functions can vary across WL methods and duration. Upon caloric restriction, ATMs recruitment increases transiently in response to WAT-derived FFAs that accumulate as the product of lipolysis and enhanced chemoattractant activity through upregulation of CCR2.[44,89] However, as lipolysis and triglyceride levels decrease with prolonged WL, so does the ATM content, presumably in response to a reduction in adipose triglyceride lipase activity.[44] Mouse studies of diet-switch-induced WL identified proliferation of ATMs with a proinflammatory signature,[50] persistent abundance of M1-like macrophages,[90] or a decrease in tissue resident macrophages.[49] Furthermore, compared with primary obesity, post-WL ATMs did not show significant changes in oxygen consumption rates, inflammatory cytokine production,[91] and phagocytosis, despite increased ROS production.[92] The persistent hyperinflammatory state upon WL has been linked to epigenomic reprogramming induced by obesity.[93] However, data collected from patients undergoing bariatric surgery show a decrease in WAT macrophage content associated with the long-term downregulation of some inflammatory gene expression.[94,95] This was validated in recent single-cell RNAseq data sets from human WL.[27,96] In addition to changes in ATM overall abundance during short-term caloric restriction–induced WL, single-cell RNAseq in mice identified a subpopulation of VAT macrophages enriched in genes associated with phagocytosis, with *Fcgr4* being the most highly upregulated gene. The gene signature of *Fcgr4*+ macrophages supports their role in adipose tissue remodeling,[97] and these macrophages were later suggested to facilitate resolution of obesity-related inflammation.[98] It is plausible that FCGR4 mediates the clearance of dying adipocytes coated with autoreactive IgGs produced by BAFF-activated B cells.[85]

Adipose T cells are particularly sensitive to obesity, as WL rarely restores T-cell balance and function. WL notably increases effector memory CD8+ T cells. However, these cells are enriched in genes related to exhaustion, such as PD-1 and TIGIT, indicating continued dysfunction despite the WL. Moreover, Tregs are not restored by WL.[49] Systemic T-cell responses that were found to be impaired in obesity are not fully recovered by WL either. For instance, a switch from a high-fat diet to a chow diet is capable of rescuing CD8+ tumor-infiltrating T-lymphocyte function in a melanoma model. However, semaglutide-induced WL failed to restore tumor immunity, suggesting divergent outcomes of metabolic reprogramming and the type of WL on immune responses.[99]

B-cell dynamics in the adipose tissue during WL are less explored. One study found reduced peripheral B cells and associated inflammatory markers, such as plasmatic IgG, and secreted cytokines in patients after bariatric surgery,[100] while another report showed restored balance of naive and memory B cells, despite increased proinflammatory gene expression 6 months post-surgery.[101]

A variety of other immune cells show parallel improvements when body weight decreases. Mast cells' genetic depletion or pharmacological stabilization has been implicated in WL.[102] Circulating neutrophils increase the release of specialized proresolving mediators during WL in humans, specifically resolvin E1,[103] indicating activation of inflammation resolution pathways.

Altogether, these findings highlight the dynamic shifts in immune cell abundance and function after WL and point to the need for detailed mechanistic studies to explain why different interventions lead to varying outcomes.

Weight Regain

Some studies have shown no modulation of ATM proportions during WR compared with primary obesity or even a reduction in total macrophage content with inverse CD11c+/CD206+ frequencies,[104,105] while others show the expansion of CD11c+ macrophages.[106] Single-cell RNAseq analysis found that increased LAM gene signatures in VAT are mainly driven by monocyte infiltration. Interestingly, LAMs' content is higher in WR compared with matched-weight primary obesity, therefore not correlating with body weight.[49] Metabolic profile of ATMs obtained from weight-cycled mice (in a model of diet-switch-induced WL) shows increased mitochondrial respiration and TNF-α production compared with the lean group, while no significant differences are observed

with primary obesity.[91] On the other hand, *Fcgr4*$^+$ macrophages that accumulate with caloric restriction revert to their obese proportions in VAT upon WR, which was associated with accelerated atherogenesis.[98] Therefore, while some studies report shifts in immune cell abundance after WR, others observe changes in function without altered numbers. These findings are not mutually exclusive; rather, they reflect the complex and

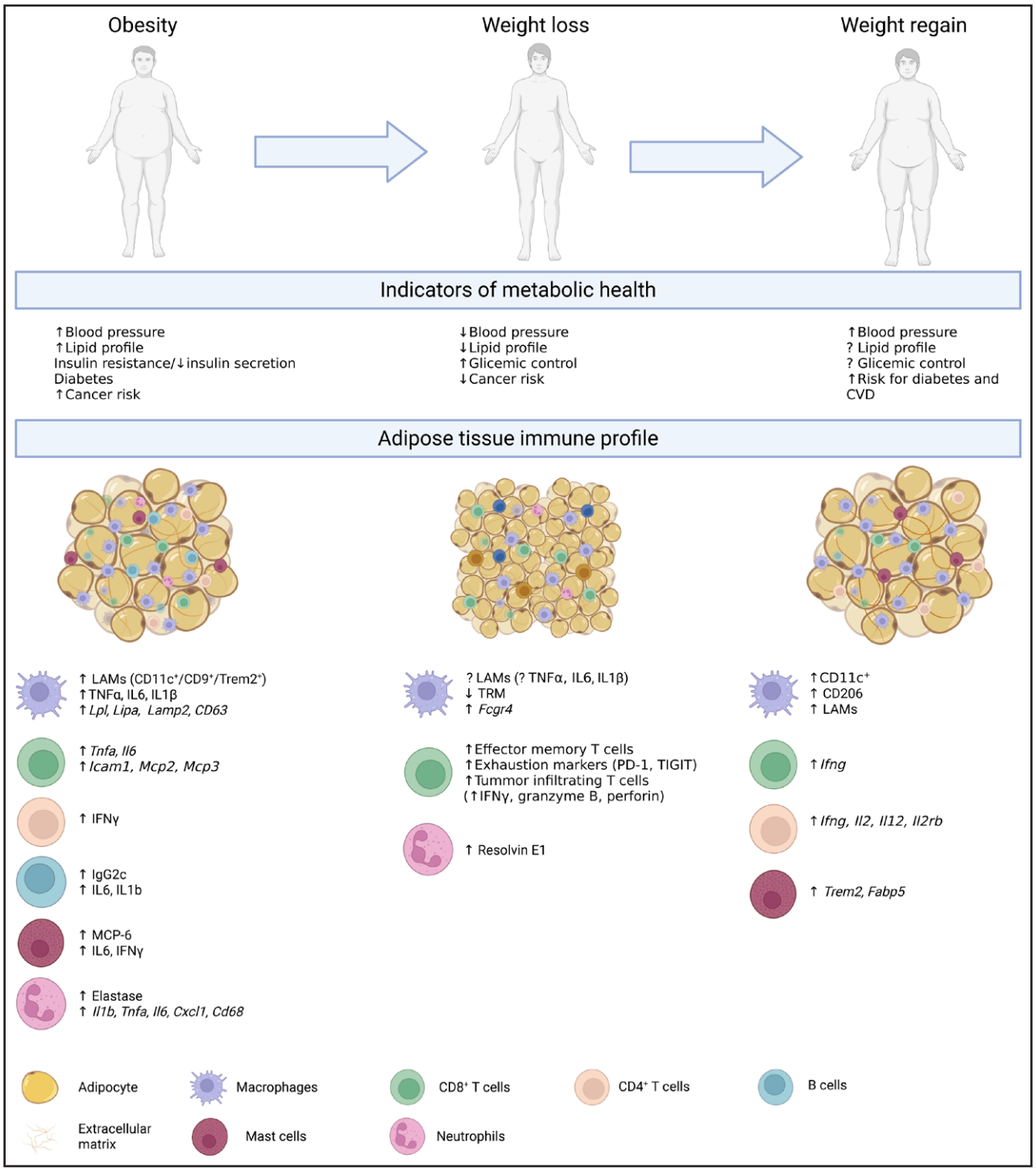

Figure. Adipose tissue dynamics in obesity, weight loss, and weight regain.
Obese adipose tissue is hypertrophic, with increased extracellular matrix deposition and immune cell infiltration, including activated macrophages having upregulated lipid-handling gene signatures. Weight loss reduces adipocyte size and extracellular matrix accumulation, while immune cells remain in the tissue, displaying a dynamic, yet not fully restorative, immune response. Weight regain enhances macrophages and T-cell proinflammatory phenotypes and increases cardiometabolic disease risk. IFN indicates interferon; IL, interleukin; LAM, lipid-associated macrophage; MCP-6, monocyte chemoattractant protein-6; and TNF-α, tumor necrosis factor-α.

context-dependent nature of immune remodeling. Comprehensive profiling that integrates both abundance and function across time points and interventions will be key to fully understanding the inflammatory outcomes of WR.

WR increases both CD4+ and CD8+ T cells with a proinflammatory signature in the VAT. In addition, a trend towards accumulation of CD8+ effector memory T cells was identified,[104] and a role for CD70, a key costimulatory molecule in memory generation, has been suggested to mediate obesogenic memory leading to worsened glucose tolerance during WR.[107]Treg abundances do not recover with WR either.[49] Interestingly, CD4+ T cells were suggested to not only accumulate in adipose with WR but also to be responsible for the associated body mass increase.[108]

Mast cells increase in WR and so does their expression of lipid-handling associated genes, including *Trem2* and *Fabp5*, although their specific functions in WAT remain mostly undetermined.[49] Whether other cell types play a role in adipose tissue inflammation during WR is yet unknown.

CONCLUDING REMARKS

WAT inflammation links obesity to metabolic dysfunction, with immune cell dynamics and function playing a pivotal role in both the progression and resolution of disease (Figure). WL ameliorates inflammation but incompletely restores adipose-immune homeostasis, while WR reignites and exacerbates inflammatory pathways, often leading to worse disease outcomes than primary obesity. The take-home message is clear: chronic inflammation in WAT is not merely a consequence of obesity but a dynamic process shaped by weight fluctuations, underscoring the importance of sustainable weight-management strategies to break the cycle of inflammation and metabolic deterioration. Critical future questions remain: how do persistent immune cell alterations during WL contribute to metabolic memory and relapse risk? Does the method of WL (eg, surgery, pharmacotherapy, or diet) shape the consequences of WL on inflammation? Can therapies targeting specific immune populations prevent adipose tissue dysfunction during WR? Elucidating the mechanisms driving heightened inflammation upon WR will be essential for developing interventions to sustain the benefits of WL. Addressing these questions will require integrating human studies with advanced animal models that capture the complexity of adipose-immune crosstalk, ultimately paving the way for novel approaches to mitigate the burden of obesity-related diseases.

ARTICLE INFORMATION

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Disclosures

None.

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