REVIEW

Putting ATM to BED: How Adipose Tissue Macrophages Are Affected by Bariatric Surgery, Exercise, and Dietary Fatty Acids

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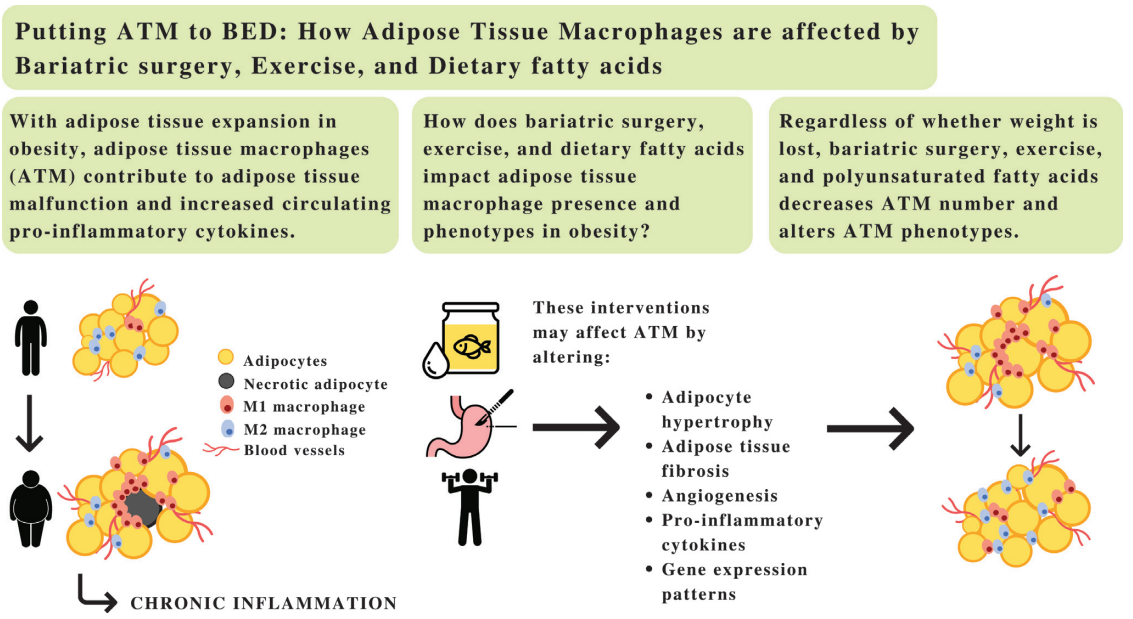
ABSTRACT

With increasing adiposity in obesity, adipose tissue macrophages contribute to adipose tissue malfunction and increased circulating proinflammatory cytokines. The chronic low-grade inflammation that occurs in obesity ultimately gives rise to a state of metainflammation that increases the risk of metabolic disease. To date, only lifestyle and surgical interventions have been shown to be somewhat effective at reversing the negative consequences of obesity and restoring adipose tissue homeostasis. Exercise, dietary interventions, and bariatric surgery result in immunomodulation, and for some individuals their effects are significant with or without weight loss. Robust evidence suggests that these interventions reduce chronic inflammation, in part, by affecting macrophage infiltration and promoting a phenotypic switch from the M1- to M2-like macrophages. The purpose of this review is to discuss the impact of dietary fatty acids, exercise, and bariatric surgery on cellular characteristics affecting adipose tissue macrophage presence and phenotypes in obesity. *Adv Nutr* 2021;12:1893–1910.

GRAPHICAL ABSTRACT



Keywords: physical activity, dietary fatty acids, bariatric surgery, macrophages, adipose tissue characteristics, meta-inflammation

Introduction

According to the WHO, the number of individuals with obesity worldwide, adults and children, has nearly tripled since 1975 (1). This increased prevalence poses a significant threat to health as individuals with obesity are more likely to develop a myriad of related conditions such as type 2 diabetes, cardiovascular diseases (CVD), and certain types of cancers (2, 3). These health consequences, in part, stem from the negative effects of excess adipose tissue accumulation leading to morphologic and functional abnormalities (2). Subsequent, endocrine, metabolic, and immune derangements follow, which contribute to the obesity-associated inflammation that is, in part, mediated by macrophages (4, 5). Indeed, macrophages can be viewed as central to tissue stress, contributing to adipose tissue malfunction and increased circulating proinflammatory cytokines as obesity progresses (5, 6). The resulting chronic inflammatory state leads to adipocyte maladaptation and subsequent increases in angiogenesis, production of extracellular matrix (ECM), macrophage infiltration, and proinflammatory response (5–7); all of the aforementioned local consequences feed in a positive feedback loop exacerbating one another.

In both human and animal models, lifestyle and surgical interventions resulting in weight loss decreased macrophage infiltration and led to a phenotypic switch of the adipose tissue macrophages (ATM) (8–13). In the case of exercise, the beneficial effects were observed regardless of weight loss. Several mechanisms have been proposed to explain the anti-inflammatory properties of physical activity and the differential properties of dietary fatty acids culminating in beneficial quantitative and qualitative changes in ATM profiles (14). The aim of this review is to discuss the impact of dietary fatty acids, exercise, and bariatric surgery on the mechanisms that affect ATM presence and phenotype in obesity.

Macrophages and Obesity

What are macrophages?

Macrophages are innate immune cells that are typically found in every tissue and have the unique ability to sense and respond to pathogens and other environmental cues. Macrophages are particularly important for: tissue repair after an injury, clearance of foreign invaders and cellular debris through phagocytosis, and normal tissue development; they are especially efficient at integrating endocrine and paracrine signals in order to respond to stimuli (15, 16). Additionally, these phagocytes are prolific communicators as they interact directly with the receptors of other tissue-resident cells, immune cells recruited during injury (e.g. T cells), and extracellular proteins (15, 16). Other noteworthy characteristic features of these monocyte-derived cells are that they are heterogeneous and exhibit high levels of plasticity.

Macrophages are able to acquire different molecular and functional phenotypes after being exposed to different bioactive molecules and environments (16, 17). Indeed, macrophages can differentiate to proinflammatory M1 or anti-inflammatory M2 cell phenotypes, though for this process to occur macrophages need to be activated or polarized (7, 18). However, how M1 and M2 macrophages come to be in the adipose tissue remains ambiguous. It has been suggested that shifts in the M1: M2 macrophage ratio occurs from the transformation of resident macrophages during the course of resolution of an injury or from the continuous recruitment of monocytes in response to tissue stress (15).

The polarization of macrophages to M1 cells is mediated by type 1 T helper cells that secrete IFN-γ or with bacterial products (e.g. LPS). M1 macrophages produce proinflammatory cytokines such as TNF-α and IL-6 and they express inducible nitric oxide synthase (iNOS), reactive oxygen species (ROS), and nitrogen intermediates (7, 18). These proinflammatory molecules have been associated with the onset of numerous diseases such as CVD or type 2 diabetes (19–21). For example, TNF-α knockout mice had improved insulin sensitivity and lower concentrations of circulating free fatty acids (22). Conversely, the polarization of macrophages to M2 cells is mediated by type 2 T helper cells that secrete IL-4 and IL-13. M2 macrophages produce anti-inflammatory cytokines such as IL-4, IL-10, and TGF-β, which block the activity of iNOS and downregulate the synthesis of proinflammatory cytokines (7, 18, 23). M2 macrophages are more often associated with wound healing, resolution of inflammation, clearing of cellular debris, regulating proliferation, precursors of angiogenesis, and remodeling of the ECM, whereas M1-like macrophages appear to promote the opposite (6, 24). It should be noted that the M1/M2 paradigm is often seen as an oversimplified dichotomous division and should rather be considered as a continuum (6, 15, 24, 25). The identification of M1 and M2 cells is also challenging as phenotype markers are not specific and may indicate other cell types. The literature therefore identifies macrophage cells as M1-like and M2-like.

Macrophages in obesity

A plethora of immune cells accumulate within the expanding adipose tissue (6), although the macrophage population remains the predominant one (26). Macrophages make up ~5–10% of the stromal vascular fraction (SVF) cells derived from adipose tissue of lean individuals, whereas in individuals with obesity, the SVF can consist of ≤40–50% macrophages (27).

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Abbreviations used: ANG, angiopoietin; ARG-1, arginase-1; ATM, adipose tissue macrophage; CCL5, chemokine (C-C motif) ligand 5; CCR, C-C chemokine receptor; CRP, C-reactive protein; CVD, cardiovascular disease; ECM, extracellular matrix; HFD, high-fat diet; HIF-1α, hypoxia-inducible factor 1-α; HR, heart rate; iNOS, inducible nitric oxide synthase; MCP-1, monocyte chemoattractant protein-1; MIP-1α, macrophage inflammatory protein-1α; ROS, reactive oxygenic species; SAT, subcutaneous adipose tissue; SVF, stromal vascular fraction; Tie-2, tyrosine-protein kinase receptor Tie-2; TLR, toll-like receptor; VEGF, vascular endothelial growth factor.

To preserve adipose tissue homeostasis and functionality, there has to be a balance between both populations of M1- and M2-like macrophages (7, 26). However, the phenotypic heterogeneity of macrophages is environment dependent (7, 18, 26). In the lean state, the balance of the macrophage population tends to shift towards the anti-inflammatory M2-like subpopulation (26). In comparison, in the obese state, the balance tilts toward the M1-like subpopulation, thus, creating a proinflammatory environment within the adipose tissue (26, 28–30). The accumulation of ATM in individuals with obesity has been linked with adipocyte and metabolic dysfunction (6, 24, 31).

Lifestyle and Surgical Interventions

Dietary fatty acids

The seminal work of Weisberg et al. (32) and Xu et al. (33) were the first to demonstrate that high-fat diets (HFDs) increase macrophage content and trafficking within the fatty depots that are associated with the development of obesity-induced insulin resistance. Indeed, fatty acids are thought to be immunomodulators of inflammatory pathways. However, not all fats are equal and different fats may have differential effects on macrophages and adipose tissue characteristics (34, 35).

Saturated Fatty Acids.

Effects of saturated fatty acids on macrophage polarization and infiltration in rodents. Studies suggest that diets rich in saturated fatty acids (SFA) are associated with inflammation as they are considered naturally occurring ligands for the toll-like receptors (TLR), which activate downstream inflammatory pathways, on both adipocytes and macrophages/monocytes (36–38). Obese rodents, fed with diets rich in SFAs (mainly from lard), have increased expression of TLRs and markers associated with macrophage infiltration (38–45) (see **Table 1**). Moreover, the activation of the TLR inflammatory pathways by an increased flux of SFAs are thought to contribute to the classical polarization of M1-like macrophages. For example, Enos et al. (42) examined the effects of 3 HFDs, differing in the percentage of total calories from saturated fat (6%, 12%, and 24%) but identical in total fat (40%), on macrophage behavior. All HFDs increased adipose tissue inflammation, but the 12% and 24% saturated fat diets increased TLR2 expression, and led to the greatest increase in M1- and M2-like macrophages (42). Additionally, several murine studies reported that feeding of SFA-rich diets worsened ROS production, the expression of adipose tissue remodeling markers [e.g. TGF-β, tissue inhibitor matrix metalloproteinase 1 (TIMP1), collagen VI, hypoxia-inducible factor 1-α (HIF-1α), and PPARγ], decreased capillary density, and increased adipocyte size, proinflammatory cytokines [e.g. IL-6, TNF-α, monocyte chemoattractant protein-1 (MCP-1), C-reactive protein (CRP)] and the number of crown-like structures (39, 41, 42, 44–52). These changes may collectively prompt the aggregation of proinflammatory macrophages. Thus, it appears that a diet rich in SFAs may trigger the development of pathogenic remodeling processes in rodents in response to the accumulation of M1-like macrophages.

Effects of saturated fatty acids on macrophage polarization and infiltration in humans. In human studies, SFAs also increased TLR genes and proinflammatory cytokines [e.g. IL-1β, IL-6, IL-8, TNF-α, chemokine (C-C motif) ligand 5 (CCL5)] in lean subjects, those with obesity, and in those with diabetes (54, 55) (see Table 1). van Dijk et al. (53) conducted a parallel controlled-feeding trial in 20 subjects who were abdominally overweight randomized to a SFA-based diet or a MUFA-based diet for 8 wk. Whole-genome microarray and histologic analysis of the adipose tissue showed that the consumption of SFAs increased proinflammatory obesity-linked gene expression including the downregulation of PPARγ and upregulation of the TLRs and macrophage marker genes (CD14 and CD163) (53). Of particular note, is that the participants' weights were not significantly different between the diet groups and did not change throughout the intervention, ruling out the cofounding factor of weight gain. The direct effects of SFA on macrophage infiltration and polarization, cellular characteristics, and adipose tissue remodeling in individuals with obesity are still poorly documented and require further investigation.

Other contributing factors to inflammation in obesity. A diet rich in SFAs may also represent a crucial first step in disturbing the gut microbiota. This disruption in the gut microbiota results in alterations in the epithelial cells of the intestinal barrier while promoting the translocation of bacteria and their cellular components into the circulation (56, 57). Consequently, a diet high in SFAs may contribute to a rise in the systemic concentration of LPS, which can act as a ligand to the TLRs on the surface of ATM and adipocytes (58–63). As such, it has been hypothesized that the translocation of LPS and bacterial metabolites may increase the release of proinflammatory cytokines, promote macrophage infiltration, and prompt a phenotype switch towards the M1-like cells (64, 65). However, a phenotypic switch has yet to be demonstrated in humans, and the influence of LPS-mediated inflammation on adipose tissue characteristics is rather unknown. Moreover, recent studies suggest that lifestyle and surgical interventions may also partially revert gut microbiota dysbiosis to improve gut health and possibly inflammation (66–68). Overall, the gut microbiota-related inflammation represents a promising alternate pathway to explain the chronic low-grade inflammation seen in individuals with obesity.

n–3 Polyunsaturated Fatty Acids.

Conversely to SFAs, n–3 PUFAs have the capacity to induce anti-inflammatory and insulin-sensitizing effects on adipocytes and their resident macrophages. These metabolic improvements have been predominantly observed with n–3 PUFA supplementation from fish oil (i.e. EPA and DHA).

TABLE 1 The effect of SFA-rich diets on macrophage infiltration and polarization in rodent and human studies

Reference	*N*	Rodents or participants	Diet	Weight change	Macrophage/ phenotype change
Coenen et al. (38, 39)	48 and 58	C57BL/6 mice	Western diet (42% fat + 0.15% cholesterol) vs. control diet 12 wk	↑	↑ infiltration of macrophages
Davis et al. (41)	75	Control male C57BL/10J mice and male Tlr-4-deficient C57BL/10ScN mice	3 experimental diets: low-fat control (LFC) vs. high-fat control (HFC) vs. high-fat palmitate (HFP) 16 wk	↑	↑ % of macrophages
Enos et al. (42)	45	Male C57BL/6 mice	5 treatment diets: 2 control diets vs. 3 HFDs (6% SF, 12% SF, and 24% SF) 16 wk	↑	↑ M1 ↑ M2 ↑ infiltration of macrophages
Prieur et al. (44)	36	Wild-type C57BL/6 male mice and *ob/ob* mice	HFD (45% fat) vs. control diet (11.5% fat) 12 wk	Ø	↑ M1 ↓ M2
Cullberg et al. (40)	N/A	Cell culture	In vitro: 3T3-L1 adipocytes and THP-1 macrophages were incubated for 24 h with FFAs (oleic, palmitic, and elaidic acids)	Ø	↑ 1.8-fold M1
Nguyen et al. (43)	40	Wild-type male C57BL/mice and *ob/obJ* male mice Cell culture	HFD (40% fat) vs. control diet (12% fat) For 1, 12, or 20 wk In vitro: RAW264.7 cells were cultured and treated with FFA (arachidonic, lauric, linoleic, oleic, and myristic acids)	Ø	↑ M1 ↑ infiltration of macrophages
van Dijk et al. (53)	20	Abdominally overweight middle-aged adults (10 male and 10 female)	2 experimental diets: SFA-rich diet (19% SFAs and 11% MUFAs) vs. MUFA-rich diet (11% SFAs and 20% MUFAs) 8 wk	Ø	↑ M1 ↑ M2

FFA, free fatty acids; HFD: High-fat diet; SF, saturated fat; lean (BMI ≤24.9); overweight (BMI 25–29.9); class I (BMI 30–34.9); class II (BMI 35–39.9); class III (BMI ≥40) ↓ : significant decrease; ↑ : significant increase; Ø: no significant change; N/A: not applicable.

The anti-inflammatory n–3 PUFAs are known endogenous ligands to PPARγ and free fatty acid receptor 4 (FFAR4), have the ability to preferentially inhibit TLR-induced pathways, and reduce the expression of proinflammatory transcription factors (69, 70–72).

Numerous studies conducted on both humans and rodents alike have demonstrated the potential advantageous effects of n–3 PUFAs on macrophage infiltration and phenotypic shifts, culminating in the amelioration of adipose tissue homeostasis. Indeed, following a dietary regimen enriched in n–3 PUFAs, the number of macrophages and specific markers of macrophage polarization for the M1- and M2-like cells fluctuated favoring an M2-dominant ratio (11, 73–92) (see **Table 2**). Itariu et al. (75) conducted an 8-wk randomized trial on 55 nondiabetic individuals with class III obesity who received either 3.36 g EPA/DHA or the equivalent amount of butterfat each day. They found that, despite no changes in M2 macrophage markers [mannose receptor C type 1 (MRC1) and CD163], pan macrophage marker (CD68), and the total number of macrophages, the expression of CD40, an M1 marker, was downregulated by n–3 PUFA treatment. Another study demonstrated that after participants with class I obesity consumed 4 g of fish oil (~3.6 g EPA and DHA) per day for 12 wk, significant decreases in total macrophage number and CD68 mRNA concentrations were observed (79). Further in vitro experiments showed that the addition of DHA to M1 macrophage cultures and cocultures with adipocytes markedly reduced the expression of MCP-1 (79). Therefore, fish oils may not only reduce macrophage abundance in adipose tissue, but also decrease the migration and infiltration of monocytes into adipose tissue (79). More recently, 3 other in vitro studies also supported these findings through similar observations and conclusions (74, 76, 77). On the other hand, in another study where individuals with overweight to class I obesity consumed 3.5% of their diet as fish oil, no difference in ATM gene expression (CD14 and CD206) was observed (93). The discrepancies in the findings may be explained by the differences in the n–3 PUFAs dose administered, the composition of the n–3 PUFAs used, or the weight status of the participants. The studies by Itariu and Spencer (75, 79) included individuals with more severe cases of obesity, which may suggest that the anti-inflammatory properties of n–3 PUFAs are more significant in individuals with greater obesity severity.

TABLE 2 The effects of n–3 PUFAs on macrophage infiltration and polarization in rodent and human studies

Reference	*N*	Rodents or participants	Diet	Weight change	Macrophage/ phenotype change
Bashir et al. (80)	25	Male C57BL/6J mice	3 experimental diets: control diet vs. HFD group (60% fat) vs. HFD + flaxseed oil (4, 8 or 16 mg/kg b.w.) 18 wk	↓	↓ M1 ↑ M2
Fan et al. (84)	47	Male C57BL/6J mice	3 experimental diets: HFD with ALA-enriched butter vs. HFD with butter lacking ALA and LA vs. HFD with ALA and LA-enriched margarine 10 wk	Ø	↓ M1 ↑ M2 ↓ infiltration of macrophages
Lopez-Vicario et al. (86)	46	Wild-type male mice and male hemizygous fat-1 mice	3 experimental diets: control diet (13% fat) vs. HFD + placebo (60% fat) vs. HFD + sEH inhibitor 16 wk	↑	↑ M2 ↓ infiltration of macrophages
Titos et al. (87)	37	Male C57BL/6J mice	Control diet (13% fat) vs. HFD (60% fat) Animals then received a placebo or DHA (4 μg/g b.w.) every day for 10 d 12 wk	Ø	↓ M1 ↑ M2 Ø total ATM
Todoric et al. (88)	49	Male C57BL/KsJ-lepr^{db}/lepr^{db} diabetic (*db/db*) mice and nondiabetic mice (*db/+*)	4 experimental diets: control diet vs. HFD + SFA + MUFA vs. HFD + n–6 PUFA vs. HFD + marine n–3 PUFA 6 wk	↑	↓ M1 ↓ infiltration of macrophages
White et al. (89)	4–14 depending on measurement	Male hemizygous *fat-1* (+/−)	Control diet vs. HFD (55% fat) 8 wk *Transgenic expression of *fat-1* n–3 fatty acid desaturase was used to endogenously produce n–3 fatty acids in HF-fed mice	Ø	↓ infiltration of macrophages ↓ crown-like structures
Chan et al. (81)	Ø	Cell culture	Low-fat diet (10% fat) vs. HFD (60% fat) 18 wk In vitro: bone marrow-derived macrophages were cultured with palmitate or palmitoleate	Ø	↑ M2 ↓ M1
Chang et al. (82)	Ø	Cell culture	In vitro: murine macrophages and human T lymphocytes were cocultured and treated with DHA	Ø	↑ M2 ↓ M1
Colson et al. (83)	24	Male C57BL/6J mice Cell culture	n–6-enriched control diet (12% fat) vs. n–3-enriched control diet (12% fat) 12 wk In vitro: THP-1 cells were cultured for differentiation experiments	Ø	↑ M2 Ø M1
De Boer et al. (91)	32	Male and female C57BL/6 mice Cell culture	4 experimental diets: HF control diet (34% fat) vs. HFD + FO (34% fat + 7.6% FO) vs. low-fat control diet (10% fat) vs. low fat + FO (10% fat + 3% FO) 12 wk In vitro: macrophages were cocultured with adipocytes	↑	↓ M1
De Boer et al. (92)	10	Male C57BL/6 mice Cell culture	Control diet (10% SO) vs. LC n–3 PUFA-enriched diet (3% FO + 7% SO) 4 wk In vitro: visceral adipose tissue were collected to create adipose tissue conditioned media and challenged with LPS to mimic acute and chronic conditions	↑	↓ M1 ↓ M2

(*Continued*)

TABLE 2 (*Continued*)

Reference	*N*	Rodents or participants	Diet	Weight change	Macrophage/ phenotype change
Liddle et al. (85)	30	Male and female C57BL/6 mice Cell culture	Control diet (10% SO) vs. treatment diet (7% SO + 3% FO) 4 wk In vitro: RAW264.7 macrophages were cocultured with LPS-stimulated CD8+ T cells/adipocytes	Ø	↓ M1 ↑ M2
Baranowski et al. (11)	21	Male *fa/fa* Zucker rats and 7 lean Zucker rats	Control diet vs. ALA-rich flaxseed oil diet 8 wk	Ø	Ø macrophage infiltration among groups
Itariu et al. (75)	55	Nondiabetic adults with class III obesity	3.36 g long-chain n–3 PUFAs/d vs. 5 g of butter/d in addition to an isocaloric diet (55% carbohydrates, 15% protein, and 30% fat) 8 wk	Ø	↓ M1 Ø M2 Ø total ATM and infiltration
Kratz et al. (93)	24	Individuals with overweight to class I obesity (8 males and 16 females)	Control diet (0.5% n–3 PUFAs) vs. n–3 PUFA-rich diet (3.5%) 14 wk	↓	Ø macrophage phenotypes and infiltration
Spencer et al. (79)	33	Adults with class I obesity (11 males and 22 females) Cell culture	4 g of n–3 fatty acid ethyl esters vs. placebo (corn oil) 12 wk In vitro: M1 macrophage culture and M1 macrophage cocultured with adipocytes were treated with DHA	Ø	↓ total ATM ↓ crown-like structures DHA decreased MCP-1 expression in cultured M1 macrophages and in cocultures of macrophages and adipocytes
Ferguson et al. (74)	N/A	Cell culture	In vitro: human SAT from lean and obese subjects were treated with EPA and/or DHA throughout differentiation or for 72 h postdifferentiation. THP-1 monocytes were added to adipocyte cocultures	Ø	↑ M2 ↓ M1
Pandurangan et al. (77)	Ø	Cell culture	In vitro: human adipocytes and macrophages were cocultured and treated with chia seed fatty acid (0–6.4 μg/mL)	Ø	↓ M1 ↓ macrophage recruitment
Montserrat-de la Paz et al. (76)	6	Healthy adult males Cell culture	Participants were all given 3 times a meal rich in SFA, MUFA or MUFA + ω-3 LC PUFA with or without niacin. In vitro: monocytes were isolated to be differentiated into naïve macrophages; TLRs were also isolated	Ø	↓ M1 ↑ M2

ALA, α-linoleic acid; ATM, adipose tissue macrophage; b.w., body weight; FO, fish oil; HF, high-fat; HFD, high-fat diet; LA, linoleic acid; LC, long chain; SAT, subcutaneous adipose tissue; sHE, soluble epoxide hydrolase; SO, safflower oil; TLR, toll-like receptor; %fat expressed based on total energy; lean (BMI ≤24.9); overweight (BMI 25–29.9); class I (BMI 30–34.9); class II (BMI 35–39.9); class III (BMI ≥40); ↓ : significant decrease; ↑ : significant increase; Ø: no significant change; N/A: not applicable.

Beneficial shifts in the M1-:M2-like macrophage ratio following n–3 PUFA supplementation may be due to a number of underlying mechanisms. Supplementation resulted in improvements in cellular stress (45, 66, 85, 94–98), metabolic profile (99), synthesis and release of anti-inflammatory mediators [i.e. IL-10, IL-4, arginase-1 (ARG-1) and adiponectin], while decreasing the secretion of proinflammatory mediators (i.e. IL-1β, IL-6, TNF-α, and MCP-1) (11, 73–75, 77, 79–81, 83–85, 100–105, 100), adipocyte enlargement (11, 12, 73, 77, 84, 95, 100, 106, 107), and the deposition of ECM and the expression of its associated markers (12, 75, 80, 85). Increased capillary density (79) and adipogenesis (73, 95, 106, 108, 109) have also been shown with supplementation. Moreover, supplementation of n–3 PUFAs downregulated the expression of important inflammatory transcription factors and receptors, such as NF-κB and TLR4, concomitant with an upregulation in adipogenic regulators [PPARγ and CCAAT-enhancer-binding protein α (C/EBPα)] (45, 73, 77,

80, 85, 90, 102, 103, 106, 109, 110). Additionally, some murine studies also observed changes in weight and fat mass loss with the previously mentioned improvements (73), whereas studies in humans showed the downregulation of inflammatory factors associated with PUFA consumption in the absence of changes in weight or body composition (73, 75, 93).

Overall, n–3 PUFA supplementation may represent a potential therapeutic avenue to improve macrophage-mediated inflammation and adipose tissue characteristics, although the effects were less potent in vivo (73, 75, 93). The inconsistent results in human studies are likely to be attributed to variability in study design, weight status of participants, and adherence as most trials are outpatient studies and rely on self-reporting. Other factors may include differences in the amount of dosage administered or methods of calculating n–3 PUFA intake (71, 73, 111). Nonetheless, further studies should continue to explore the role of n–3 PUFAs in mediating ATM infiltration and phenotype.

Physical activity

Lack of exercise and prolonged sedentary behaviors are important catalysts for a cluster of metabolic and chronic diseases, whereas regular exercise may prevent or delay the progression of insulin resistance, hypertension, CVD, and diabetes (112, 113). Although numerous studies have denoted that the salutary effects of exercise are independent of weight loss (113–116); significant weight loss may amplify the exercise-induced benefits and have a greater impact on the inflammatory markers in humans (9, 117, 118). In fact, physical activity was shown to induce cellular and molecular changes in the adipose tissue in a way that alleviates the low-grade chronic inflammation that accompanies obesity (8–10, 119–121). The underlying mechanisms that contribute to the exercise-induced anti-inflammatory responses have not been completely elucidated. A major contributor to the reduction in inflammation accompanying exercise may reside in the mediation of ATM (14, 113, 116, 122, 123).

The effects of exercise on macrophage infiltration and phenotypes.

Exercise, with or without weight loss, may decrease inflammation via promoting a phenotypic switching from M1 to M2 macrophages while simultaneously diminishing the trafficking of the macrophages within the adipose tissue. The early work of Kawanishi et al. (47) demonstrated that 16 wk of cardiovascular exercise training (12–20 m/min, 60 min/d, and 5 times/wk) in mice with obesity reduced M1-like and increased M2-like macrophage mRNA expression in adipose tissue such that the M1-:M2-like ratio was ∼50% lower with the exercise intervention relative to control. Quantification of macrophages in adipose tissue by flow cytometry also showed that exercise decreased both the proportion and absolute number of M1-like (CD11c+) macrophages (124). Another study found that in comparison to continuous training (steady state running at 20 m/min), aerobic interval training (3-min bouts at 40 m/min, interspersed by 3-min active recovery at 20 m/min on a treadmill with 15% incline, repeated 6 times per session) has been shown to result in greater increases in the number of M2-like macrophages (181% versus 122%) in mesenteric adipose tissue (48). More recent murine studies have demonstrated diminished infiltration and phenotypic shifts in macrophages (48, 125–130) (see **Table 3**).

In humans, few studies have looked at the direct impact of exercise on the polarization of the macrophage populations (9, 119, 131) (see Table 3). These studies have found exercise-induced shifts towards a predominant M2-like phenotype. An 8-wk low-intensity exercise intervention (walking 10,000 steps 3 times/wk) in adults with overweight and class I obesity showed that exercise was associated with a ∼2.1-fold upregulation of M2 markers and a downregulation of M1 markers independent of weight loss (132). Additionally, Auerbach et al. (119) and Bruun et al. (9) corroborated the previous findings through an exercise-induced weight-loss protocol suggesting that pronounced weight loss may also further affect macrophage infiltration and phenotype resulting in an anti-inflammatory milieu within adipose tissue.

Mechanisms altering macrophage infiltration and phenotypes in exercise.

Exercise decreases expression of proinflammatory and chemotactic signals. There is a growing body of evidence suggesting that exercise decreases the expression of proinflammatory and chemotactic cytokines involved in the recruitment of macrophages and monocytes (14, 113, 116). Among all the cytokines known to potentially contribute to inflammation within the adipose tissue and the chemotaxis of macrophages, TNF-α, IL-6, and MCP-1 appear to be the best studied and were consistently shown to have lower levels of expression following exercise treatment in humans, mice, and rats (8–10, 117, 120, 121, 124, 126, 127, 132, 133–144). Baturcam et al. (133) found that 3-mo supervised exercise {combination of moderate intensity [50–80% of max heart rate (HR)] aerobic exercise and resistance training using either a treadmill or cycling 3–5 times/wk} significantly reduced the expression of both CCL5 and C-C chemokine receptor type 5 (CCR5) in the adipose tissue of individuals with class I to class II obesity with decreases in the concentrations of the proinflammatory markers TNF-α, IL-6, and protein and c-jun NH2 terminal kinase (P-JNK). Complementing these findings, Barry et al. (8) demonstrated that both high-intensity interval training (at 90% of HR_{peak}, for 1 min interspersed with 1 min of low-intensity recovery periods, progressing from 4 to 10 intervals) and moderate-intensity continuous training (at 65% of HR_{peak}, progressing from 20 to 50 min) in humans, in the absence of weight and fat mass loss, altered leukocyte trafficking through the downregulation of inflammatory chemokine receptors such as CCR2, CCR5, and C-X-C chemokine receptor type 2 (CXCR2). In humans and rodents, exercise has also been associated with an increase in the expression and release

TABLE 3 The effects of exercise on macrophage infiltration and polarization in rodent and human studies

Reference	*N*	Rodents or participants	Exercise intervention	Weight change	Macrophage/ phenotype change
Kawanishi et al. (47, 124)	40	Male C57BL/6 mice	Treadmill running 12–20 m/min × 60 min/d 16 wk	Ø	↓ M1 ↑ M2 ↓ number of macrophages
Macpherson et al. (126)	27	Male C57BL/6 mice	Treadmill running 3 d × 15 min/d at 15 m/min acclimation 2 h at 15 m/min with 5% incline	Ø	↓ M1 ↑ M2 ↓ infiltration of M1-like macrophages
Linden et al. (125)	113	Male C57Bl6/J mice	Treadmill running 40 min/d at 12 m/min with 8% incline 4, 8, or 12 wk	Ø	↓ M1 ↑ M2 ↓ infiltration of macrophages
Luo et al. (128)	54	Male C57BL/6H mice	Treadmill running 45% of peak running speed, with 5% incline, 1 h/d, 6 d/wk 8 wk	↓	↓ M1 ↑ M2
Baek et al. (129)	49	Male C57BL/6 J mice	Treadmill running at 10 m/min for 60 min Mice ran at different intensities from week 2 to week 8	↓	↓ M1 ↑ M2
Oliveira et al. (127)	24	Male Wistar rats	Swimming 2-d swimming × 10 min/d acclimation 3 h of exercise with a 45-min rest period	Ø	↓ M1 ↑ M2 Ø in infiltration
Kolahdouzi et al. (48)	48	Male Wistar rats	Treadmill running 5 d/wk 3 groups: Sedentary vs. CT vs. AIT 10 wk	CT: ↓ 30% weight loss AIT: ↓ 40% weight loss	↓ M1 ↑ M2 ↓ number of macrophages
Shanaki et al. (130)	45	Male Wistar rats	Treadmill running (HIIT or CT) 5 d/wk 10 wk	↓	↓ M1 ↑ M2
Bruun et al. (9)	27	Individuals with class III obesity (15 females and 12 males)	2–3 h of exercise 5 d/wk 15 wk Included a diet	↓ ~ 14% weight loss	↓ ~55% M1 ↓ ~40% number of macrophages
Auerbach et al. (119)	60	Healthy and overweight adult men	Endurance training for 7 d/wk 4 groups: training-induced weight loss (T) vs. diet-induced weight loss (D) vs. training and increased diet without weight loss (T-iD) vs. control (C) 12 wk	↓ 6% weight loss in the endurance training group (T)	↑ 2.5-fold M2 Ø macrophage number
Yakeu et al. (132)	17	Healthy overweight adults (9 males and 8 females)	Walking on treadmill 10,000 steps 3 times/wk for 75 min 8 wk	Ø	↓ M1 ↑ M2
Ruffino et al. (146)	19	Overweight adult women	Walking on treadmill 3 times/wk for 45 min 8 wk	↓	↓ M1 ↑ M2
Lee et al. (131)	26	Sedentary lean or overweight men with or without dysglycemia	2 sessions of strength training and 2 sessions of spinning 4 h/wk 12 wk	↓	Ø M1 ↓ M2 ↓ infiltration of macrophages

AIT, aerobic-interval training; CT, continuous training; HIIT, high-intensity interval training; lean (BMI ≤24.9); overweight (BMI 25–29.9); class I (BMI 30–34.9); class II (BMI 35–39.9); class III (BMI ≥40); ↓ : significant decrease; ↑ : significant increase; Ø no significant change.

of anti-inflammatory signals such as IL-10, IL-6, ARG-1, and adiponectin (9, 14, 115, 117, 126, 136, 137, 145). Despite the fact that the positive effects of exercise have been observed in the absence of weight loss, weight loss may compound the benefits. An exercise study (aerobic training, 60–75 min/session and 3 times/wk) found that compared with subjects in the lowest tertile (–3%) of weight loss, those in the highest tertile of weight loss (–14.5% weight loss) had larger decreases in macrophage inflammatory protein-1α (MIP-1α) and IL-15 and greater increases in adiponectin

(117). Aside from TNF-α, IL-6, and MCP-1, several other cytokines associated with inflammation were shown to have a reduced expression following an exercise intervention such as CCL5, plasminogen activator inhibitor-1 (PAI-1), MIP-1α, CRP, chemerin, IFN-γ, IL-1, IL-8, IL-15, and IL-18, which may also further improve the chronic low-grade inflammation seen in adipose tissue (9, 117, 120, 121, 127, 133, 134, 136, 140).

Exercise affects adipose tissue characteristics. In addition to decreasing proinflammatory and chemotactic signals associated with macrophage recruitment, exercise also directly affects adipose tissue characteristics that are associated with the recruitment and phenotypic changes of ATM. A recent murine study by Kolahdouzi et al. (48) found that aerobic interval training improved adipose tissue dysfunction induced by a HFD through increasing the number of M2-like cells and capillary density while decreasing the total number of crown-like structures and mean adipocyte size (48). Multiple murine studies have also demonstrated beneficial changes in cellularity that may be associated with decreased ATMs. Moreover, several key features of dysfunctional adipose tissue are improved such as lipid and glucose metabolism (134, 135, 147), improved mitochondrial activity and biogenesis (147–150), decreased expression of apoptotic signals (151), decreased expression of angiogenesis precursors (152–157), increased capillary density (48), reduced accumulation of fibrotic depots (10, 46), and reduced adipocyte size (48, 134, 148, 158, 159). Similar findings were also made in human studies where lipid metabolism, mean adipocyte size, adipose tissue fibrosis, and proangiogenic responses were improved following exercise training with or without weight loss (139, 160, 161).

Exercise modifies gene expression patterns. Underlying the mechanisms of the potent anti-inflammatory properties of exercise are tremendous gene expression alterations that may have a direct impact on chronic low-grade inflammation as well as the ubiquitous proinflammatory macrophage infiltration seen in adipose tissue of individuals with obesity (148, 162). Aside from varying the gene expression of pro- and anti-inflammatory cytokines, angiogenic regulators, ECM precursors, markers of mitochondrial activity, and lipid and glucose metabolism (9, 46, 120, 147, 153), physical activity also affects the gene expression of key adipogenic regulators (such as PPARs) and well-characterized immune receptors that modulate inflammatory pathways (like the TLRs) (14).

Several studies highlight the crucial immunomodulating role of PPARs, more specifically PPARγ, in regulating adipose tissue inflammation by promoting the infiltration of M2 macrophages in humans and mice (163–165). Macrophage-specific deletion of the PPARγ gene (163) and upregulation of PPARγ by rosiglitazone (164) in mice demonstrated the role of PPARγ in M2-like macrophage activation. Exercise upregulates PPARγ expression and its related signaling events in adipose tissue and monocytes/macrophages of humans, mice, and rats (146, 166–171), favoring a phenotypic shift towards the M2-like macrophages. In a human study, Yakeu et al. (132) found that low-intensity exercise (walking 10,000 steps 3 times/wk) shares similar effects to the pharmacological activation of PPARγ and that a ~4–5-fold increase in PPARγ activity and expression coincided with a ~2.1-fold increase in the M2-like macrophage marker (CD14).

TLRs are a class of membrane proteins that play an important role in the innate immune system by initiating key downstream inflammatory pathways through recognition of exogenous and endogenous ligands (172). TLRs, especially TLR2 and TLR4, are present on the cell surface of adipocytes and macrophages [especially M1-like macrophages (173)] and play a pivotal role in obesity-related pathogenesis, including in the development of insulin resistance, and the metabolic syndrome (14, 172). The TLR family are activated by a vast array of ligands, many of which are higher in obesity such as LPS (a marker of gut permeability), oxidized LDLs, and SFAs. The binding of a bioactive molecule to TLRs, results in the activation of NF-κB and the release of proinflammatory cytokines (6, 113, 172). The pivotal role of TLR4 in obesity-associated pathogenesis was demonstrated from the observations that TLR4 knockout mice were protected from the adverse effects of high-fat feeding with attenuated inflammation and macrophage infiltration (113, 172). In parallel with TLR4 knockout mice, exercise training resulted in similar metabolic improvements by decreasing the expression of TLR4 on the cell surface of monocytes and macrophages (138, 174–178); in some cases, TLR4 expression and activity was reduced by $\leq$35% following exercise interventions (178). In mice and rats, the reduced expression of TLR4 on the surface of the adipocytes and/or SVF cells following exercise correlates with the phenotypic shift in ATM from the M1- to the M2-like phenotype, and reduced macrophage infiltration (47, 127, 177, 179, 180). However, despite the decreased expression of TLR4 activity following exercise training in humans (136, 178, 181–187), more questions remain to be explored regarding the role of TLR4 in macrophage polarization and infiltration. To our knowledge, most human studies on TLR4 expression following exercise examined monocytes rather than ATM directly and results were sometimes inconclusive (188). Given that monocytes are precursor cells of macrophages, it is plausible that the decreased TLR4 expression may also coincide with changes in the phenotype of macrophages as seen in rodents. Further investigations examining the effects of exercise on TLR4 expression in humans is required.

Overall, what remains unknown is which form of exercise training is best to mitigate ATM infiltration and phenotypes in obesity. Several studies indicate that higher intensities and combined training (e.g. combined aerobic and resistance training versus aerobic or resistance training alone) better improved obesity-associated inflammation (116, 189). However, the comparison of these training modalities has not been investigated in ATM infiltration. Future studies should further explore the mechanisms driving macrophage infiltration and polarization in response to exercise and

focus on the training modalities (duration, type, volume, and intensity) that are best at mitigating ATM inflammation.

Bariatric surgery

Often, when first-line treatment options, such as dietary interventions and exercise programs, are not enough to induce significant weight loss or metabolic improvements in individuals with obesity, many turn to bariatric surgery. Indeed, bariatric surgery is one of the most powerful tools to induce weight loss; a worldwide study from 31 countries found that the surgeries induced an overall 1 y-weight loss of ∼30.5% (190). Aside from the effectiveness for weight loss, bariatric surgery is often accompanied with weight-loss-dependent metabolic improvements including the mitigation of ATM inflammation.

Effects of surgery on macrophage populations.

Several studies observed significant reductions in macrophage number up to a year after surgery using the CD68 marker (30, 191–194) (see **Table 4**). Cancello et al. (30) found an ∼12% reduction in the number of ATM after surgery, which is likely due to the decreased expression of chemotactic genes. Bariatric surgery was also found to alter the phenotype of macrophages favoring a shift towards M2-like macrophages (195–201) (see Table 4). Aron-Wisnewsky et al. (195) found that in premenopausal women without diabetes, the ratio of M1-: M2-like (CD40+: CD206+) macrophages was 2-fold lower in subcutaneous adipose tissue (SAT) after 3 mo than before surgery due to a simultaneous decrease of CD40+ and an increase of CD206+ macrophages. Similarly, others have found an increased presence of M2- over M1-like macrophages in the adipose tissue ≤12 to 24 mo after surgery (198, 199). Altogether, these studies suggest that the immune and inflammatory profile of bariatric surgery patients may take years to reach new baseline levels. Overall, robust evidence indicates quantitative and qualitative changes in ATM populations following weight loss surgery.

Mechanisms affecting macrophage infiltration and polarization after bariatric surgery.

Weight loss by bariatric surgery decreases expression of proinflammatory cytokines and chemotactic signals. An extensive amount of research has studied how bariatric surgery affects cytokine-related macrophage chemotaxis and polarization. Although unclear, current literature suggests that bariatric surgery may improve the inflammatory status of individuals with obesity. Two previous reviews (13, 202) listed several cytokines and their variations at different time points after bariatric surgery. An example being that CRP and leptin unanimously decreased, adiponectin constantly increased, and TNF-α remained unchanged at all time points after surgery. As for the other highly expressed cytokines during obesity such as IL-1β, IL-6, IL-10, and MCP-1, results are inconsistent even ≤2 y postoperation. For instance, 3 mo after surgery, Xu et al. (203) observed improved insulin sensitivity, increased AMP-activated protein kinase (AMPK) expression, and decreased oxidative stress with no changes in IL-1β, TNF-α, and IL-10 levels in patients. Such discrepancies were hypothesized to be the result of the presurgical presence of diabetes and the baseline level of insulin sensitivity (204–206). For example, a greater CRP reduction was observed after surgery in ex-obese patients with diabetes compared with those who were not diabetic (206). Moreover, the inflammatory state of visceral adipose tissue and the patients' nutritional status presurgery were also suggested to influence the postsurgical inflammation state (202). Overall, the inconsistent effects of surgically induced weight loss on cytokine fluctuation remain unexplained due to a lack of convincing results. The long-term effects of cytokine secretion on health of individuals with obesity after surgery are unknown.

Effects of surgery on adipocyte morphology. Appreciable weight loss after bariatric surgery results in extensive adipose tissue remodeling on multiple levels, implicating mechanisms underlying adipose tissue plasticity. The architecture and homeostasis of the adipose tissue and the cells composing the SVF are tightly regulated by the equilibrium between hypertrophy and hyperplasia, which may be improved following weight loss resulting in diminished macrophage-mediated inflammation. Several studies analyzing either the volume or the area of the adipocytes found that postsurgery fat cells were smaller, ultimately approaching measurements similar to lean controls (191, 194, 207–209). For example, Casmatra et al. (210) and Löfgren et al. (211) reported a postsurgical reduction of fat cell area by 50% and volume by 43%, respectively. Additionally, Andersson et al. (212) reported significant adipocyte volume loss after surgery, but with no changes in cell number. Thus, suggesting that adipocyte atrophy is the main plastic event taking place during weight loss induced by surgery.

Effects of surgery on angiogenesis in adipose tissue. Adipose tissue expansion is intricately dependent on vasculature, which is increased during obesity. Indeed, angiogenesis is a response to adipose tissue hypoxia that results from its expansion and poor blood supply. As such, angiogenic markers like vascular endothelial growth factor (VEGF), angiopoietin-1 (ANG-1), ANG2, tyrosine-protein kinase receptor Tie-2 (Tie-2), and HIF-1α are overexpressed in obesity which potentiate proangiogenic responses to improve tissue blood supply, inflammation, and ultimately adipocyte dysfunction (213). Bariatric surgery may induce significant reduction of these angiogenic markers while concomitantly decreasing the recruitment of M1-like macrophages. Weiwiora et al. (214) studied the concentrations of circulating angiogenesis biomarkers [ANG-2, granulocyte colony-stimulating factor (G-CSF), hepatocyte growth factor (HGF), platelet endothelial cell adhesion molecule-1 (PECAM-1), VEGF, and follistatin] preoperatively and 12 mo after surgery in 24 patients with class III obesity. The expression levels of these angiogenic markers were all downregulated postsurgery and their changes were dependent upon the

TABLE 4 The effects of bariatric surgery on macrophage infiltration and polarization at different time points after surgery in human studies

Reference	*N*	Participants	Macrophage/phenotype change				
			≤1 mo	3 mo	6 mo	12 mo	24 mo
Cancello et al. (30)	24	17 women with class III obesity and 7 lean women		↓ 12% ATM			
Aghamohammadzadeh et al. (191)	22	15 adults with class III obesity and 7 lean individuals			↓ ATM		
Haluzikova et al. (192)	32	17 women with class III obesity and 15 lean women			↑ ATM surpassing baseline concentrations (before surgery)	↓ ATM	↓ ATM (concentration similar to control)
Trachta et al. (193)	31	13 nondiabetic women with class III obesity and 18 lean women			↑ ATM	↓ ATM	In SAT: ↓ ATM (concentrations similar to baseline)
Liu et al. (198)	118	Individuals with class III obesity				↓ ATM ↑ M2	
Aron-Wisnewsky et al. (195)	26	16 women with class III obesity and 10 lean women		↓ M1 ↑ M2 ↓ 2-fold M1/M2			
Garcia-Rubio et al. (197)	71	43 individuals with class III obesity and 28 exmorbidly obese individuals with class I obesity				↓ M1-like cells in SAT and VAT	
Cinkajzlova et al. (196)	83	32 nondiabetic individuals with class III obesity and 32 individuals with class III obesity and diabetes and 19 lean controls	In plasma: ↓ M2 In SVF of SAT: ↓ M2		In plasma: ↓ M2 In SVF of SAT: ↓ M2		
Moreno-Navarrete et al. (199)	6	Women with class III obesity and normal glucose metabolism					↑ M2
Hagman et al. (200)	17	Men and women with obesity class II and III	↑ M1 ↑ M2			↑ M1 ↑ M2	
Hess et al. (201)	40	20 individuals with class III obesity and 20 lean controls		↓ ∼1.1% M1 ↑ ∼10.1% M2			

ATM, adipose tissue macrophages; SAT, subcutaneous adipose tissue; SVF, stromal vascular fraction; VAT: visceral adipose tissue; lean (BMI ≤24.9); class I (BMI 30–34.9); class II (BMI 35–39.9); class III (BMI ≥40); ↓ : significant decrease; ↑ : significant increase; Ø: no significant change or not applicable.

amount of weight loss. Similarly, Figueroa-Vega et al. (213) found that before surgery the concentrations of proangiogenic markers (ANG-1, ANG-2, Tie-2, and HIF-1α) were overexpressed (both in serum and adipose tissue), which correlated with an increased number of infiltrating M1-like macrophages expressing angiogenic receptor Tie-2 especially in SAT (213). At 6 mo after surgery, the expression of these markers was significantly reduced and correlated with a diminished number of infiltrating M1-like macrophages (213). Therefore, angiogenesis may not only be important for adipose tissue expansion, but it may also represent another pathway to explain the chronic inflammation observed in obesity, which is alleviated by weight loss surgery. However, the knowledge of angiogenic mechanisms and its impact on adipose tissue dysfunction and health postsurgery is still rudimentary and requires more research.

Effects of surgery on adipose tissue fibrosis. Fibrosis is a hallmark feature of adipose tissue inflammation as it is triggered and exacerbated by macrophage infiltration (215, 216). However, the reversibility of adipose tissue fibrosis after surgery-induced weight loss is unclear. To our knowledge, only 2 studies have directly examined fibrosis pre- and post-bariatric surgery and both have concluded that levels of fibrosis remained unchanged and persisted despite the significant weight loss in most participants from 6 mo to $\leq$2 y after surgery (194, 217). In contrast, Liu et al. (198) and Reggio et al. (218) observed a downregulation in the expression levels of genes encoding markers of adipose tissue fibrosis from 6 mo to 1 y postsurgery (198, 218). Moreover, Liu et al. (198) observed a positive relationship between collagen accumulation and the number of M2-like (CD163+) cells prior to surgery, indicating a role in the generation of fibrosis in obese SAT. However, this M2-to-pericellular collagen accumulation relation became a negative correlation at the 1-y-follow-up despite the moderate increase in the number of CD163+ cells. Overall, the evolution of fibrosis postsurgery, the role played by ECM proteins, and their link with ATM during weight loss are poorly documented.

Conclusion and Future Prospects

In this review, we discussed the impact of dietary fatty acids, exercise, and bariatric surgery on cellular characteristics affecting ATM presence and phenotypes in obesity. We have shown that dietary fatty acids, exercise training, and bariatric surgery decrease ATM and induce a phenotypic switch to M2-like macrophages through modifying a number of potential mechanisms. In the case of the type of fat ingested and exercise, improvements in ATM occurred regardless of weight loss. These interventions modify ATM by affecting key adipose tissue characteristics such as adipocyte size, adipose tissue fibrosis, angiogenesis, and cytokine and adipokine secretion. Future studies should focus on gaining a better understanding of the underlying mechanisms and consequences of the reduction in macrophage presence and phenotypes, especially in humans. Understanding the events contributing to the pathogenesis of obesity may allow for the development of potential new therapies against obesity and its associated comorbidities.

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