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Is Adipose Tissue Inflammation the Culprit of Obesity-Associated Comorbidities?

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ABSTRACT

In individuals with obesity, the onset of chronic comorbidities coincides with the excessive accumulation of adipose tissue in various tissue beds. As obesity progresses, adipose tissue becomes increasingly dysfunctional causing chronic low-grade inflammation. Indeed, adipose tissue inflammation, which partially stems from macrophage infiltration and expression of macrophage-derived cytokines, has local and systemic consequences on health and increases the likelihood of developing obesity-associated comorbidities. In addition, cellular changes driven by macrophages may also further aggravate both adipose tissue dysfunction and inflammation, thus contributing to the onset and progression of several comorbidities including type 2 diabetes, cardiovascular diseases, nonalcoholic fatty liver disease, osteoarthritis, some cancers, and dementia. The purpose of this review is to discuss how adipose tissue inflammation relates and contributes to the pathogenesis of obesity-associated comorbidities.

1 | Introduction

It is estimated that by 2030, more people will be overweight or obese than not [1]. Of particular concern is that obesity greatly augments the risk of developing life-threatening diseases, such as type 2 diabetes (T2D), cardiovascular diseases (CVD), and certain cancers [2]. In obesity, the excessive accumulation of adipose tissue (AT) results in morphologic, functional, and metabolic abnormalities causing AT dysfunction and whole-body metabolic derangements [2]. Notable predominant features of AT dysfunction are adipocyte hypertrophy, fibrosis, impaired angiogenesis and adipogenesis, and immune cell infiltration, especially macrophages.

Abbreviations: AMPK, AMP-activated protein kinase; AT, Adipose tissue; ATM, Adipose tissue macrophages; BMI, Body mass index; CRP, C-reactive protein; CT, Computed tomography; CVD, Cardiovascular diseases; ECM, Extracellular matrix; GSK3-β, Glycogen synthase kinase-3 β; HDL, High-density lipoprotein; HER2+, Human epidermal growth factor receptor 2 positive; IFP, Infrapatellar fat pad; IL, Interleukin; IR, Insulin resistance; IRS-1, Insulin receptor substrate-1; JNK-α, C-Jun N-terminal kinase; MAFLD, Metabolic dysfunction–associated fatty liver disease; MAPK, Mitogen-activated protein kinase; NAFLD, Nonalcoholic fatty liver disease; NF-κB, Nuclear factor kappa B; NLRP-3, Nod-like receptor protein 3; OA, Osteoarthritis; PPAR-α, Peroxisome proliferator–activated receptor alpha; SAT, Subcutaneous adipose tissue; SOCS, Suppressor of cytokine signaling; STAT3, Signal transducer and activator of transcription factor 3; T2D, Type 2 diabetes; TNF-α, Tumor necrosis factor-alpha; VAT, Visceral adipose tissue; WHR, Waist-to-hip ratio.

Anjalee I. Wanasinghe indicates shared first authorship.

Imbalances in anti- and pro-inflammatory cytokine secretion from both adipocytes and adipose tissue macrophages (ATM) have demonstrable impact on insulin resistance (IR), ectopic fat deposition leading to the nonalcoholic fatty disease (NAFLD), CVD, deteriorating joint health, carcinogenesis, and brain health [3–8]. Furthermore, the contribution of regional AT depots, such as femoral and gluteal fatty depots, toward obesity-associated comorbidities remains unclear. Building on prior reviews that have focused on AT inflammation in relation to insulin resistance and metabolic syndrome, this review provides a novel synthesis of recent evidence linking obesity-associated AT inflammation to a broader range of comorbidities including CVD, NAFLD, osteoarthritis (OA), breast and colorectal cancers, and cognitive disorders. With this expanded framework, the aim of this review is to discuss the local and systemic consequences of regional AT inflammation as a potential underlying mechanism for obesity-associated comorbidities.

2 | Adipose Tissue Inflammation and Obesity

Adipose tissue plays a pivotal role in whole-body energy reserves and metabolism. Most notably, AT from various depots function as hormone-secreting organs important to whole-body metabolism [9, 10]. The architecture and homeostasis of AT are intricately regulated by the equilibrium between hypertrophy and hyperplasia, which are altered, in part, by weight fluctuations [11]. Indeed, in the context of obesity, positive energy balance requires extensive AT remodeling on multiple levels, implicating mechanisms underlying AT plasticity, especially hypertrophy [11]. The AT microenvironment undergoes dramatic quantitative and qualitative changes, ultimately promoting inflammation [2, 12, 13].

2.1 | The Pathogenic Potential of Adipose Tissue Remodeling

In response to chronic positive energy balance, AT expands to accommodate excess lipid via adipocyte hypertrophy and hyperplasia, thus maintaining blood glucose and fatty acid concentrations below toxic levels [14]. This AT expansion is accompanied by acute local inflammation. Acute increases in AT inflammation have been shown to be beneficial - with studies in mice showing that suppression of inflammation in the initial stages of expansion increases insulin resistance, ectopic lipid accumulation, and systemic inflammation [15, 16]. However, chronic inflammation in AT appears to perturb AT function, contributing to metabolic derangements [4, 7, 17, 18]. Pro-inflammatory changes of AT include increased angiogenic responses, reduced adipogenesis, cellular senescence, excessive extracellular matrix (ECM) synthesis, dysregulated secretion of adipocytokines, and subcellular damage [2, 12, 19–23], which may contribute to the development of pro-inflammatory milieu within AT (Figure 1).

Regional AT depots exhibit distinct characteristics in response to obesity because of their anatomical and functional differences (Table 1). For example, VAT is more metabolically active compared to other AT depots, while gluteofemoral AT is metabolically protective against obesity-associated diseases. We have previously reviewed the sexual dimorphism in AT and found that regional differences may partially explain the different patterns of disease development in males versus females. Of note, the hyperplastic ability of female AT in all regions may protect them against AT inflammation compared to males [83].

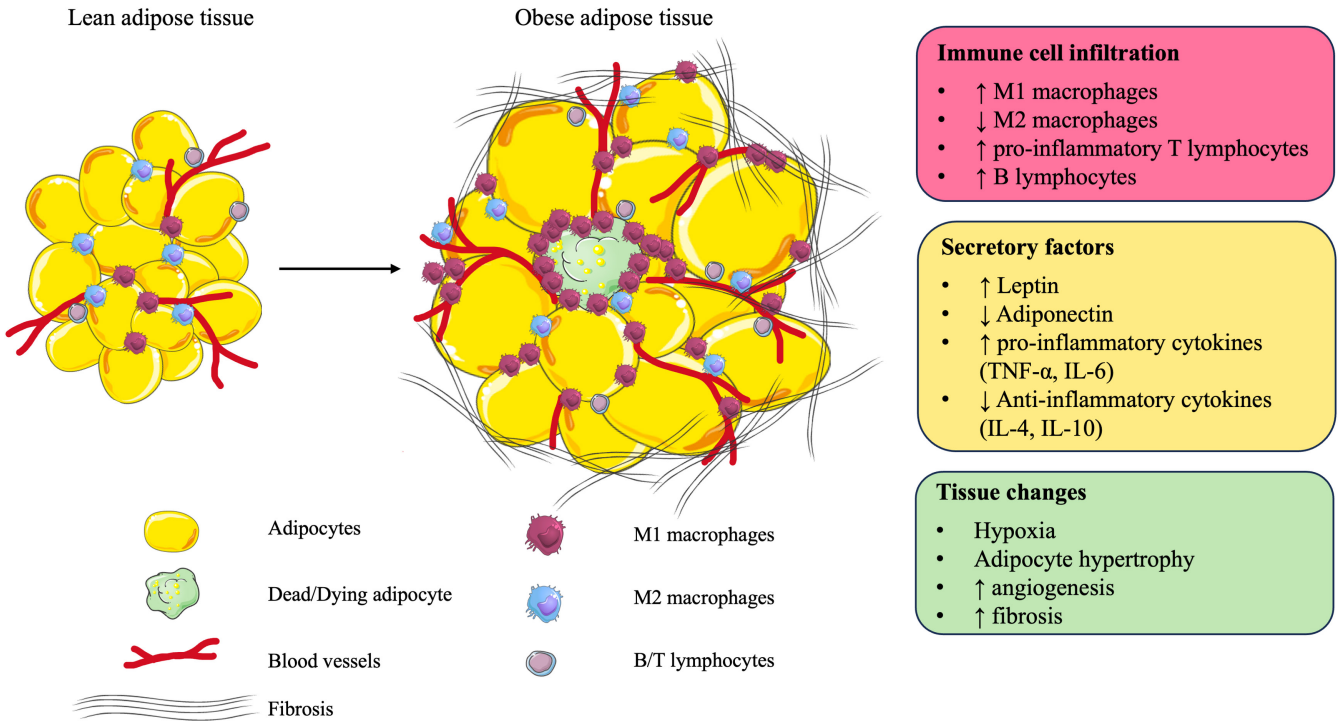

FIGURE 1 | Adipose tissue remodeling in obesity. Excessive accumulation of adipose tissue leads to adipocyte hypertrophy, hypoxia, immune cell infiltration, increased secretion of pro-inflammatory adipokines and cytokines, fibrosis, impaired angiogenesis, and distrupted adipogenesis resulting in a pro-inflammatory microenvironment.

TABLE 1 | Effects of obesity on regional adipose tissue characteristics and their implications.

	VAT	abSAT	gfSAT	Breast AT	EAT
Adipocytes	↑↑ size [11, 24–27]	↑ size [11, 27, 32, 41, 42]	↑size [11, 41, 47, 48]	↑ size [50–53]	Ø in size [55, 56]
Adipocyte size	(♂ > ♀) [28]	(♂ > ♀) [28, 43]	(gfSAT > abSAT > VAT)	∝ breast CA risk [50, 52, 54]	♂ ∝ BMI [57]
	∝ IR [24, 25, 27, 29–32]	∝ IR [30, 40, 42]	(♂ > ♀) [49]		♀ Ø [57]
	∝ CVD [31, 33–35]	∝ NAFLD [36, 37, 44]			∝ CVD [58, 59]
	∝ NFLD [17, 29, 31, 36–39]	∝ CVD [45]			↓ size vs. other depots [55, 59]
	∝ dyslipidemia [33, 40]	SAT > VAT [11, 26, 31, 33, 35, 46]			(SAT > EAT = PAT)
Hyperplasia	↑ hyperplasia [24]	↑ hyperplasia	↑ hyperplasia		
	↓ doubling time [60]	(♂ < ♀) [28]	[14, 20]		
	−∝ IR [40]	−∝ IR [40]	VAT > gfSAT > abSAT		
Senescence	↑ senescent cells [14, 60]	↑ senescent cells [61]	Ø senescent cells [61]		
		(♂ = ♀)	(♂ < ♀)		
Immune cells	↑↑ ATM [24, 46, 62–65].	↑ ATM [41, 72]	↓ ATM (vs. other depots) [41, 48]	↑ CLS [50, 51, 75]	CD68 + ∝ CVD [58, 79, 80]
Macrophages	↑ pro-inflammatory ATM [62, 66].	VAT > SAT [30, 46, 64, 66, 68]	↓ M1:M2 [48]	∝ breast CA risk [50, 51, 75, 76]	M1:M2 ratio ∝ CVD [79]
	↑ M1:M2 [48, 65]	↑ M1 ATMs [73]		↑ M1 ATMs [52]	
	CD68 + ∝ IR [30, 67, 68]	(♂ = ♀)		CD68 + −∝ [insulin] and receptor level [77]	
	ATM ∝ Dyslipidemia [63, 68]	AbSAT > gfSAT		↑ M2 (protumerigenic) ATM	
	ATM ∝ NAFLD [68–71]	CD68 + ATM ∝ IR [67]		∝ breast CA risk [78]	
		CLS ∝ NAFLD [74]			
		M1-CLS ♀ < ♂ [25]			
T cells	↑ CD8 + T cell [81]	↓ Th1, Th2, and Th17 vs. VAT [81]	↑ Total T cell in ♀ [73]	FA oxidation mediated activation of CD8 + T cells ∝ breast CA risk [84]	Ø Total T cells [85, 86]
	↑ Th1, Th2, and Th17 [81]	↑ Tregs [82, 83]	(gfSAT > abSAT)		
	↓ T regs [82, 83]		Ø in ♂		
Secretory function	↑ Pro-inflammatory adipokines and cytokines [60, 64, 71, 82, 87]	Pro-inflammatory cytokine VAT > SAT [82, 87, 88]	Adipokines > cytokines [89]	↑ Estrogen sensivity [82]	↑ Pro-inflammatory adipocytokine secretion [85]
		cytokines > adipokines [89]		CA-associated adipocytes → ↑ pro-inflammatory adipocytokine secretion [90]	VAT>EAT>SAT [85, 91, 92]
					pro-inflammatory cytokine and adipokine expression ∝ CAD [92–94]
					adiponectin expression −∝ CVD [92, 93, 95]

(Continues)

TABLE 1 | (Continued)

	VAT	abSAT	gfSAT	Breast AT	EAT
Lipid metabolism Lipogenesis	↑ LPL activity [96] abnormal upregulation of adipogenic genes [60]	↑ Capacity to uptake of circulating FFA and TGs [14, 24, 29, 88]. Hypertrophic obesity ∝ ↓ adipogenesis [23] ↑ LPL activity [49, 96] (♂ < ♀) [49]	↑ Fat storage capacity [97] ↑ LPL activity [49] abSAT < gfAT < fmSAT (♂ < ♀) ↑ metabolically protective lipokine palmitoleate production (gfSAT > abSAT) [98]	↑ Lipid accumulation → lipotoxicity [99]	↑ FA synthesis and incorporation vs. other depots [59] ↑ fat accumulation → lipotoxicity [29]
Lipolysis	↑ FFAs and TGs release into portal circulation [14, 24, 29] ↑ HSL activity [96]	↑ HSL activity [96] VAT = SAT	↓ Lipolytic activity [100–102] ↓ HSL and GH receptors (abSAT > gfSAT) [103, 104]	CA-associated adipocytes → ↑ lipolytic activity and deliver FFA to breast cancer cells [99]	

Abbreviations: abSAT, abdominal subcutaneous adipose tissue; ATM, adipose tissue macrophages; BMI, body mass index; breast AT, breast adipose tissue; breast CA, breast cancer; CAD, coronary artery disease; CVD, cardiovascular disease; CLS, crown-like structures; EAT, epicardial adipose tissue; FFA, free fatty acids; gfSAT, gluteofemoral adipose tissue; GH, growth hormone; HSL, hormone sensitive lipase; IR, insulin resistance; LPL, lipoprotein lipase; NFLD, nonalcoholic fatty liver disease; PAT, pericardial adipose tissue; T regs, T regulatory cells; TG, triglycerides; Th1, T helper 1 cells; Th2, T helper 2 cells; Th 17, T helper 17 cells; VAT, visceral adipose tissue; ↑, significant increase; ↓, significant decrease; Ø, no significant change; ♂, male; ♀, female; ∝, positive correlation; −∝, negative correlation.

2.2 | Adipose Tissue Macrophages and Obesity

Of all immune cells in AT, macrophages are the most abundant comprising up to 50% of stromovascular cells in AT from humans with obesity [62, 63]. These macrophages have been shown to play an important role in AT remodeling and have been implicated in metabolic disease risk. ATMs are heterogeneous and exhibit high levels of plasticity; they can acquire multiple molecular and immunophenotypes in response to various stimuli in their surrounding microenvironment [105, 106]. Functionally, macrophages can be divided into two broad categories: M1 and M2 macrophages. M1 macrophages are typically considered pro-inflammatory as they secrete IL-1β, IL-6, IL-8, IL-12, and TNF-α and play an important role in tissue injury [107, 108]. Oppositely, M2 macrophages are generally anti-inflammatory as they secrete IL-4, IL-13, and IL-10 and are associated with wound healing, resolution of inflammation, clearing of cellular debris, regulating proliferation, and remodeling of the ECM [81, 107, 108]. In humans, M1 macrophages tend to express cell surface markers such as CD11c, CD14, and CD40, whereas M2 macrophages most commonly express CD163 and CD206 [108]. While this M1/M2 macrophage paradigm was an initially useful model, recent advances suggest that macrophages may be more phenotypically diverse with a more complex range of activation states. The different subsets of pro- and anti-inflammatory macrophages have been extensively reviewed by Russo et al. [108]. The diversity of ATM implies that the pathogenesis of obesity-associated comorbidities characterized by macrophage-mediated inflammation may be more complex than previously thought with different subsets of macrophages playing different roles in obesity pathology. Although we acknowledge this diversity in ATM, for the purpose of this review, ATM will be examined as the simplified dichotomous division between M1 and M2 macrophages since there is little literature that classifies ATM into more specific phenotypes.

In obesity, the macrophages appear to exhibit a phenotypic shift to favor M1 over M2 macrophages, contributing to the development of a pro-inflammatory microenvironment in AT [109] (Figure 1). The degree of AT inflammation and macrophage infiltration is depot dependent. Visceral adipose tissue (VAT) was shown to contain more macrophages of all phenotypes and express higher levels of pro-inflammatory cytokines in comparison to subcutaneous adipose tissue (SAT), highlighting the unique inflammatory signature of VAT that may affect disease risk differently [24, 29] (Table 1). Accordingly, compared to SAT, the accumulation of macrophages in VAT is more often associated with cellular and metabolic derangements that lead to AT dysfunction and possibly the pathogenesis of obesity-associated comorbidities [24, 110] (Figure 2).

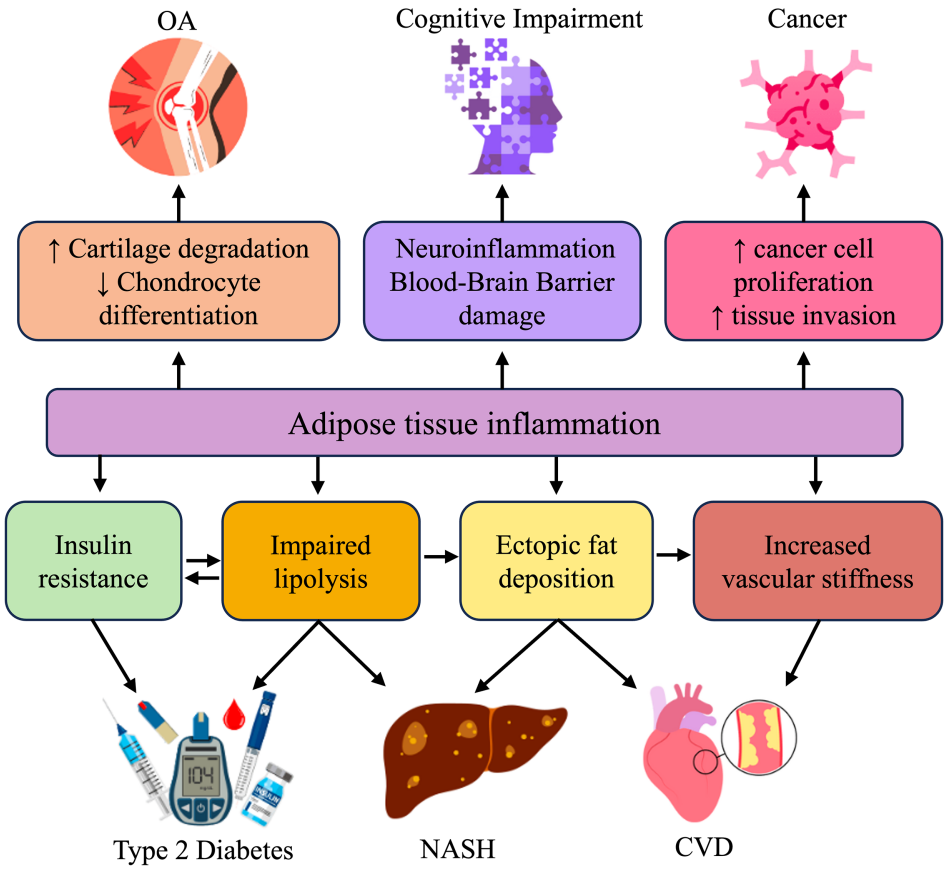

FIGURE 2 | Adipose tissue inflammation leads to obesity-associated comorbidities. An overview of the main pathogenic processes that lead to multiple metabolic and pathological conditions. Adipose tissue inflammation promotes insulin resistance, impaired lipolysis, ectopic fat deposition, and increased vascular stiffness, leading to diseases such as type 2 diabetes, nonalcoholic fatty liver disease (NAFLD), and cardiovascular diseases (CVD). Each of these conditions is interconnected with the inflammatory processes rooted in adipose tissue dysfunction, highlighting its role in systemic metabolic and degenerative diseases.

3 | Type 2 Diabetes

3.1 | Markers of Adipose Tissue Dysfunction and Insulin Resistance

There is a large body of evidence indicating that changes in AT characteristics are important catalysts in the development of insulin resistance and consequently T2D in individuals with obesity. Indeed, adipocyte hypertrophy [2, 25, 26, 28, 30, 31, 33, 41, 46, 110–112], AT fibrosis [3, 11, 113–122], hypoxia [123–125], angiogenesis [123–125], and AT senescence [61, 126–134] have all been associated with IR and other metabolic derangements in AT. Of these characteristics, adipocyte hypertrophy is one of the best studied AT characteristics and is especially well linked with IR. Several studies have observed that adipocyte hypertrophy is associated with a multitude of markers of cardiometabolic health including IR or sensitivity; these correlations were found to be more significant in VAT than in SAT [28, 110]. Although most studies emphasize the harmful effects of VAT accumulation, research from our group and others showed that VAT and SAT both contribute to metabolic health in different ways [46, 83, 135].

3.2 | Circulatory Adipokines and Cytokines on Insulin Resistance

The role of AT-derived adipokines and cytokines in IR has been extensively studied and is well established. Leptin is an important homeostatic adipokine that regulates energy balance, metabolism, immune function, and many other physiological processes of the body [136]. In obesity, higher levels of leptin promote IR in adipocytes by disrupting insulin signaling pathways, such as mitogen-activated protein kinase (MAPK) activity, glycogen synthase kinase 3- β (GSK-3β) phosphorylation, and insulin receptor tyrosine phosphorylation [137]. Obesity also increases the expression of suppressor of cytokine signaling 3 (SOCS3) protein, which is thought to upregulate leptin and insulin signaling [138]. In addition, chronically high levels of leptin may lead to leptin resistance in the hypothalamus, ultimately disrupting glucose homeostasis [139]. Although significantly higher leptin levels were observed in females when compared to males, in both sexes, leptin levels were independently associated with the degree of IR [140, 141]. However, Klöting et al. in a study done on both males and females, observed no significant differences in leptin levels in individuals with insulin-resistant obesity versus insulin-sensitive obesity [30]. Such differences could be partly due to the selective leptin and insulin resistance in various tissues and the complex interplay between the leptin and insulin signaling pathways [142, 143].

In contrast with leptin, reductions in AT adiponectin secretion with obesity decrease AMP-activated protein kinase (AMPK) and peroxisome proliferator–activator receptor-α (PPAR-α) activity. Lowering of AMPK and PPAR-α activity results in disrupted glucose and lipid metabolism, increasing IR [144, 145]. Low adiponectin levels along with high leptin levels may also indirectly affect the insulin receptor function via activation of pro-inflammatory pathways, such as nuclear factor-kappa B (NF-κB) [145]. Moreover, low adiponectin levels promote lipid accumulation, lipotoxicity, and oxidative stress, which further impairs insulin sensitivity [146, 147]. In line with the aforementioned findings, significantly lower adiponectin levels were observed in individuals with insulin-resistant obesity versus insulin-sensitive obesity [30]. This observation did not differ between males and females even though females had higher adiponectin levels compared to males in both groups [30].

Increased levels of pro-inflammatory cytokines also promote IR by interfering with insulin signaling pathways. Tumor necrosis factor-α (TNF-α) inhibits insulin receptor activity by increasing serine phosphorylation and reducing tyrosine phosphorylation of insulin receptor substrate proteins, while also activating pro-inflammatory pathways such as NF-κB and JNK (c-Jun N-terminal kinase) [148, 149]. Similarly, interleukin-6 (IL-6) disrupts insulin signaling through the JAK/STAT pathway, leading to SOCS protein–mediated inhibition and insulin receptor substrate-1 (IRS-1) degradation. Additionally, TNF-α and IL-6 promote oxidative stress and mitochondrial dysfunction, which exacerbate metabolic disturbances [148]. IL-6 also enhances hepatic glucose production, contributing to hyperglycemia and worsening IR [150]. As such, the effects of obesity-derived adipokines and cytokines on insulin resistance are brought on by complex, overlapping intracellular signaling pathways.

3.3 | Adipose Tissue Macrophages and Insulin Resistance

Both preclinical and clinical studies have demonstrated the link between macrophage number, phenotype, and insulin resistance [151, 152]. For example, in male mice, Patsouris et al. [153] demonstrated that the depletion of CD11c + cells (M1-like macrophages) from epididymal fat pads caused rapid normalization of insulin sensitivity along with decreases in local and systemic inflammatory markers [153]. In humans, however, the relationship between pro-inflammatory macrophages and IR is more ambiguous. Nonetheless, several studies found that in adults and children with obesity, IR was related to increased infiltration of ATM, including both M1- and M2-like macrophages, as well as a greater number of crown-like structures [30, 66, 67, 69, 72, 111, 112, 154, 155]. Kunz et al. [155] found that across a wide range of body mass index (BMI) (20.5–45.8 kg/m^2), CD68+, and CD206 + macrophages and local and systemic markers of inflammation were associated with reduced insulin sensitivity in abdominal SAT of nondiabetic, middle-aged adults. In line with the previous study, Fjeldborg et al. [72] found that while all macrophage markers (CD68, CD14, CD163, and CD206) were elevated in SAT of sedentary male and female participants with obesity, only the increases of CD163 + (M2-like) macrophages correlated with IR. Therefore, regardless of phenotype, macrophage infiltration in general may contribute toward IR. Furthermore, because skeletal muscle is the largest driver of systemic IR, compared to AT and liver [156], ATMs may contribute to skeletal muscle IR, particularly through the release of pro-inflammatory cytokines [155].

However, other studies suggest that macrophage-mediated inflammation in AT may not be associated with IR. Jia et al. [25] demonstrated that in 97 participants with obesity, metabolic parameters, including IR, did not associate with abdominal

subcutaneous CD68 + (total ATM), CD14 + (M1-like), and CD206 + (M2-like) ATM density. These findings remained consistent across sexes despite males having significantly higher crown-like structures containing CD14 + (M1-like) ATMs when compared to females [25]. Their analysis revealed that indexes of IR (systemic and AT IR) were predicted by body composition and adipocyte size [25]. Similarly, Espinosa de Ycaza et al. [41] observed that in individuals with obesity and normal weight, AT IR did not correlate with either abdominal or femoral SAT ATM markers (CD68, CD14, and CD206). Instead, it was found that femoral fat cell size was a stronger predictor of the ability of insulin to suppress AT lipolysis [41]. However, the study population in consideration was predominantly female (72%) [41], and the effects of ATM on IR may differ depending on the sex differences [83]. Thus, the role of ATM in IR remains unclear, and further studies are required to understand the diverse roles of ATM in different subpopulations.

3.4 | Regional Adipose Tissue Macrophages and Their Association With Insulin Resistance

Only a few studies have compared how SAT versus VAT macrophages are associated with IR in adults with obesity [30, 66, 67, 111] (Table 1). While femoral and gluteal adipose tissue were not examined, the presence of ATM in both SAT and VAT may be an important contributor to IR and thus, the onset of T2D. In bariatric surgery candidates with insulin resistance, omental AT mass, concentrations of inflammatory markers, as well as the number of CD68 + macrophages, were higher than in those with insulin sensitivity [30]; these differences were not observed in abdominal SAT. Similarly, Hardy et al. [111] found that in bariatric surgery candidates, omental CD68 + cell infiltration significantly correlated with IR [111]. Conversely, in females with moderate-to-severe obesity (BMI 39–56 kg/m^2), CD11c + cells (M1-like macrophages) density was greater in SAT than in VAT and correlated more strongly with IR [66]. Bigornia et al. [67] found that the increased presence of CD68 + crown-like structures in both SAT and VAT correlated with markers of systemic IR [67]. Thus, it appears that visceral ATMs may play a more significant role in IR than subcutaneous ATMs except in severe obesity. In a study involving healthy individuals who followed an overfeeding diet (1250 kcal/day, 45% fat) for 28 days, insulin sensitivity decreased by 11% without significant changes in abdominal subcutaneous ATM or adipocyte size [157]. Similarly, Jia et al.[25] suggest that the effects of subcutaneous ATM on IR may be confounded by adipocyte size/body composition, given the variability in predictive values across different adipocyte sizes [25]. The hyperplastic capacity of SAT may play a protective role in ATM-mediated AT inflammation. However, in cases of severe obesity where the hyperplastic capacity of SAT is diminished, subcutaneous ATMs may contribute to a greater degree of AT inflammation and IR.

In summary, AT dysfunction characterized by morphological and functional changes as well as increased macrophage infiltration may play an important role in the development of local and systemic IR. However, more mechanistic studies are necessary to establish causality. In addition, the contribution of femoral and gluteal fatty depots to IR should be further explored as most studies focused only on subcutaneous abdominal and VAT.

4 | Cardiovascular Diseases

The association between adiposity and CVD has been widely studied and is well established. It has been found that CVD risk increases by 10% for every 5 kg/m^2 increase in BMI [158]. Numerous studies have found that inflammation from different fatty depots has differential effects on the incidence of CVD. Of all AT depots, the accumulation of VAT may be the greatest risk factor for the onset and progression of CVD [159, 160]. Further, the accumulation of epicardial fat and SAT are likely significant contributors to the pathogenesis of CVD [161, 162].

4.1 | Circulatory Adipokines and Cytokines on Cardiovascular Disease

The chronic low-grade inflammation associated with obesity and the imbalances in adipokine secretion appear to affect atherogenesis. High levels of leptin were independently associated with increased CVD risk, incidence of congestive cardiac failure, and CVD hazard ratio [163, 164]. Importantly, these associations remained significant in a cohort of over 6000 participants after adjusting for several potentially confounding factors, including age, race, hypertension, smoking, dyslipidemia, diabetes, and both total and central adiposity [164]. Leptin appears to promote atherosclerosis, thrombosis, and endothelial dysfunction in mouse models [165]. Although the precise mechanisms are not fully understood, it is believed that leptin may attenuate coronary vasoreactivity [166] and increase hepatic high-density lipoprotein (HDL) cholesterol uptake, thereby lowering serum HDL levels in humans [167]. Leptin has also been found to impair endothelial relaxation in resistance vessels and enhance the pressor response to angiotensin II, which is a potent vasoconstrictor [168]. Such effects of leptin may lead to vascular stiffness, which ultimately results in hypertension and increased CVD risk [168].

Conversely, adiponectin may be protective for CVD, and high adiponectin levels are associated with reduced risk of nonfatal CVD and increased event-free survival ratio [169–171]. The protective effects of adiponectin against atherosclerosis are elicited via several mechanisms. Adiponectin has been shown to activate the NF-κB pathway and prevent cytokine-induced endothelial activation [172]. Furthermore, *in vitro*, adiponectin enhanced cholesterol efflux and reduced foam cell formation in macrophages extracted from patients with diabetes [173]. While adiponectin appears to play a protective role in the pathogenesis of CVD, others have found that higher adiponectin levels are also considered an independent predictor of mortality associated with CVD, possibly because of compensatory upregulation following a cardiovascular event [169, 174].

In obesity, the increase in leptin and reduction of adiponectin may also promote M1-like macrophage activation in AT, thereby increasing the secretion of pro-inflammatory cytokines such as TNF-α, IL-6, and IL-1 [175]. Elevated levels of TNF-α and IL-6 were associated with a greater risk of myocardial infarction,

with the risk being even more pronounced among individuals with obesity [176–180]. TNF-α can enhance atherosclerosis by increasing transcytosis of lipoprotein across endothelial cells via the activation of NF-κB and PPAR-γ pathways [175, 181]. Similarly, IL-6 also augmented the risk of CVD via activation of endothelial and smooth muscle cells, and increased macrophage recruitment, and lipid accumulation [182–185].

4.2 | Regional Adiposity on Cardiovascular Disease

Strong associations between increased VAT mass and CVD risk factors such as dyslipidemia, increased blood pressure, and IR are well established [186–191]. Several studies also showed an association between SAT mass and CVD risk [186, 188, 190, 192]. This association was nonsignificant in some studies when adjusted for age, BMI, and waist circumference [186]. However, when it comes to AT, it might not only be the quantity that should be considered in predicting CVD risk but also quality. Computed tomography (CT) attenuation has been used as a marker of AT quality. Lower CT attenuation of VAT and SAT was strongly associated with greater BMI levels and increased fat accumulation in both males and females [160, 193]. Lower CT attenuation in AT is strongly correlated with pro-inflammatory biomarkers such as C-reactive protein (CRP), leptin, and insulin in patients who had CVD risk factors [194]. Furthermore, reduced VAT and SAT attenuation were associated with increased risk of CVD, and this association was stronger in VAT compared to SAT [160, 187, 193–195]. Apart from SAT and VAT, increased intrahepatic fat also showed a greater correlation with cardiometabolic risk factors [186].

Adipocyte hypertrophy in VAT strongly correlates with cardiometabolic risk factors in individuals with overweight and obesity [31–35, 40, 42]. A 10% increase in the omental adipocyte size increased the risk of hypertriglyceridemia by fourfold in women with obesity [33]. However, in individuals with morbid obesity, larger adipocytes in SAT were strongly associated with cardiometabolic risk factors when compared to VAT [45]. Such differences may arise because of the limited expandability of SAT depots [28, 45, 196]. For instance, VAT but not SAT adipocyte size correlated strongly with measures of adiposity such as BMI, waist circumference, and body fat percentage [35]. We hypothesize that larger adipocytes in SAT are an indicator of AT dysfunction potentially affecting lipid storage [40, 197, 198] (Table 1).

Epicardial AT also plays an important role in CVD risk as this AT is adjacent to cardiac tissue and shares the same blood supply, facilitating the uptake of epicardial AT secretions by cardiac tissue [91, 199–201]. Increasing epicardial AT volume was found to be associated with the development of high-risk coronary artery plaques [201]. Additionally, epicardial AT volume and thickness were also found to be associated with an increased risk of cardiac death, myocardial infarction, and atrial fibrillation [200].

Both obesity and abdominal obesity have strong positive associations with epicardial AT volume [202, 203], however, the effects of obesity on epicardial adipocyte size is less clear and may vary by sex (Table 1). Greater epicardial adipocyte size significantly correlated with CVD risk [58, 59]. Though some studies showed no effect of obesity on epicardial adipocyte size [55, 56], when sex is considered Waddel et al. found an independent relationship between adipocyte size and in males but not in females [57]. Compared to noncoronary artery disease patients, patients with coronary artery disease had greater epicardial AT, gene expression of pro-inflammatory cytokines (TNF-α, leptin, IL-6, IL-1β, and visfatin), and lower levels of adiponectin [91–95]. In patients with coronary artery disease, epicardial AT appears to secrete two times the amount of leptin and adiponectin compared to subcutaneous and mediastinal AT [91]. In contrast, epicardial AT from coronary artery disease patients secreted less TNF-α, IL-6, leptin, and visfatin compared to abdominal VAT [92]. Although obesity is associated with greater epicardial AT volume, the aforementioned studies did not consider overall adiposity in their analyses. Thus, further studies are required to understand the specific effects of obesity on epicardial AT inflammation.

4.3 | Regional Adipose Tissue Macrophages in Cardiovascular Disease

A study that compared SAT and three VAT depots (mesenteric, peri-aortic, and omental) in patients who underwent abdominal aortic surgery [64] and found reduced concentrations and numbers of adipokines and ATMs in SAT. Compared to patients without coronary artery disease, patients with coronary artery disease have also been shown to have increased macrophage infiltration (CD68+), especially of the M1-like phenotypes (CD11c+) in epicardial AT [58, 79]. Moreover, in patients with chronic heart failure, epicardial AT is typically thinner, with higher macrophage infiltration (CD68+), and impaired angiogenesis [80]. An ex vivo study compared the effects of SAT and VAT exosomes on atherogenesis and observed that VAT exosomes markedly increased the generation of macrophage foam cells. Visceral adipose tissue exosomes also significantly induced an M1 phenotype transition and TNF-α and IL-6 secretion compared to SAT exosomes [87]. These findings suggest a larger influence of epicardial AT and VAT in macrophage-mediated inflammation leading to atherogenesis compared to SAT.

5 | Nonalcoholic Fatty Liver Disease

Recently, the term “metabolic dysfunction–associated fatty liver disease (MAFLD)” has been coined to describe fatty liver disease of metabolic origin. As the studies reviewed generally refer to nonalcoholic fatty liver disease (NAFLD), we will continue to use NAFLD with the understanding that these cases likely include patients with MAFLD.

5.1 | Cellular and Metabolic Changes in Adipose Tissue Contribute to NAFLD

Nonalcoholic fatty liver disease is increasingly prevalent in individuals with obesity and T2D, and as obesity progresses, so does the severity of the disease. A hallmark feature of NAFLD is the ectopic deposition of fatty tissue among hepatocytes leading to morphologic and functional changes in the liver [204].

Recent studies in humans with NAFLD depict morphological alterations and mediators of AT dysfunction that may aggravate AT inflammation and potentiate hepatic injuries [36–39, 44, 70, 205]. Indeed, several groups found that patients with obesity and NAFLD had significantly higher mean adipocyte size in both SAT and VAT, indicating that adipocyte hypertrophy is associated with fatty liver and consequently NAFLD [36–39, 44]. For instance, Osorio-Conles et al. [38] observed that in female adults with both severe obesity and NAFLD, VAT, but not SAT cell area, were 20% greater in comparison to those without NAFLD. They also found that NAFLD was associated with a lower abundance of smaller adipocytes (16% less) and higher abundance of larger adipocytes (55% more) in VAT relative to those with obesity only.

In addition to adipocyte hypertrophy, other studies also demonstrated the link between NAFLD and other features of AT dysfunction such as AT fibrosis, impaired microvascular density, and markers of hypoxia, apoptosis, and inflammation in VAT [70, 205]. There is a large body of evidence demonstrating that the dysregulated secretion of adipokines and adipocytokines, most notably leptin, adiponectin, TNF-α, and IL-6, is a determinant of NAFLD progression [17, 206]. As such, macrophages and their pro-inflammatory cytokines may have the ability to dysregulate lipolysis, increasing the release of fatty acids into circulation and causing fat deposition to ectopic locations such as the liver [207–209]. Furthermore, numerous studies indicate that NAFLD progression is sex specific, which may be in part due to differences in body fat mass partitioning and regional AT characteristics [36, 70, 205, 207]. For example, Leven et al. [205] showed that the profibrotic deposition of ECM in VAT of adults with both obesity and NAFLD was sex specific with females displaying a greater degree of fibrosis than males. Accordingly, AT dysfunction or the cellular changes associated with AT remodeling may be potential biomarkers for the presence and severity of NAFLD.

5.2 | Adipose Tissue Macrophages and NAFLD

Direct evidence of the role of ATM as a potential contributor to NAFLD was recently highlighted by Bijnen et al. [210] who observed that compared with lean-transplanted mice, transplanting donor VAT from obese to lean mice increased hepatic macrophage content and worsened liver injury. Moreover, ATM depletion prior to VAT transplantation markedly reduced hepatic macrophage accumulation. Another murine study also found that surgical removal of inflamed epididymal fatty tissue after 12 weeks of high-fat diet significantly attenuated the progression of NAFLD, as well as the expression of inflammatory cytokines [211].

In humans, patients with NAFLD had heightened AT inflammation with greater infiltration of inflammatory immune cells, especially macrophages [38, 68–71, 74, 210, 212, 213]. In several studies, adult participants with NAFLD consistently had increased proportions of pro-inflammatory macrophages in VAT, which correlated positively with the hepatic infiltration of immune cells and fibro-inflammatory lesions [38, 68–71, 210, 212]. For example, Cancello et al. [68] found that in 55 bariatric surgery candidates with at least two comorbidities out of T2D, hypertension, or dyslipidemia, there were twice as many HAM56 + macrophages in omental VAT than in abdominal SAT and that increased accumulation of macrophages in omental AT correlated strongly with hepatic lesions. While these studies found associations between VAT macrophages and NAFLD, two others found that both fat compartments had differentially expressed genes associated with AT inflammation and NAFLD, suggesting that these tissue beds may contribute differently to NAFLD progression [38, 71]. Fuchs et al. [213] also demonstrated that the total number of CD206 + CD11c + macrophages along with the expression of several cytokines in abdominal SAT was greater in those with both obesity and NAFLD compared to lean and obese individuals with normal intrahepatic triglyceride content. As such, it is likely that SAT inflammation may also play a role in the pathogenesis of NAFLD.

Overall, macrophage-mediated inflammation and changes in AT characteristics may represent a possible mechanism affecting NAFLD progression and severity. However, most studies focused on VAT only and very few have investigated the contribution of SAT in NAFLD. As SAT represents approximately 80% of fat mass, any disturbances in SAT metabolism, morphology, and overall homeostasis may have notable local and systemic consequences on health. Future studies may want to include subcutaneous depots from various anatomical locations to provide a larger picture of how AT inflammation and dysfunction affect NAFLD.

6 | Osteoarthritis

6.1 | Adipose Tissue–Derived Markers and Osteoarthritis

Osteoarthritis (OA) is one of the most common joint diseases characterized mainly by the progressive degeneration of articular joints [214]. Emerging evidence suggests that changes in the inflammatory profiles of systemic AT via the increased secretion of adipokines and adipocytokines may damage joint tissue [5, 215]. Furthermore, the infrapatellar fat pad (IFP), a naturally occurring fatty depot within the knee joint, was found to present quintessential markers of AT dysfunction leading to inflammation and damage in joint tissue [5, 215]. A vast array of murine studies has investigated whether pro-inflammatory cytokines and adipokines were mediators of OA pathogenesis. Consistently, OA progression and severity were positively associated with not only body fat mass, but also several adipokines and cytokines, most notably leptin and adiponectin [215]. Further evidence of the contribution of adipokines in OA pathogenesis was highlighted by Griffin et al. [216] who found that regardless of obesity severity and body fat levels, the absence of the leptin gene or receptor in mice prevented the development of knee OA.

Findings in humans with both OA and obesity are consistent with preclinical studies. Adipokine levels, such as leptin, adiponectin, visfatin, and resistin, in both serum and synovial fluid correlated with OA onset, progression, and radiographic severity; they were also found to upregulate downstream inflammatory pathways, cartilage degradation, infiltration of immune cells in joint tissue, mesenchymal cell differentiation, and

chondrocyte de-differentiation [217, 218]. The deleterious effects of adipokines and several other inflammatory molecules in the development of OA were extensively discussed in recent reviews [217, 218].

Newly published studies also identified adipokines as potential biomarkers for pain in those with both OA and obesity in a relationship that may be sex dependent [219–221]. For instance, in 596 women who were overweight to obese with knee or hip OA, higher pain intensity was significantly associated with higher leptin-to-adiponectin ratio independently of radiographic severity [221]. Interestingly, in the 267 males participating in this study, no correlation between pain intensity and the biomarkers of AT inflammation was found [221]. Similarly, a meta-analysis of 11 studies found that increased leptin expression was strongly associated with OA severity, especially in females compared to males [222].

6.2 | The Inflammation of the Intra–Articular Adipose Tissue in Osteoarthritis

Intra–articular AT are highly innervated fat pads located within joints of several articulations found between the synovium and the joint capsule [217]. The most studied and largest intra–articular AT is the IFP located in the knee. Although the physiological role played by intra–articular fatty depots is thought to be protective [217], recent research has found that the IFP may have detrimental effects in OA progression. Histologically, intra–articular AT individuals who are overweight or obese with OA were found to closely resemble VAT and differ from SAT in terms of adipocyte size, fibrotic depots, resident immune cell profile, and inflammatory gene expression [223–225]. Harasymowicz et al. [226] found that in patients with end-stage OA and moderate-to-severe obesity, intra–articular AT had a greater proportion of hypertrophied adipocytes, marked increases in fibrosis, and increased expression of the TLR4 gene while the expression of PPARγ was reduced when compared to lean individuals with OA. Thus, IFP adipocytes are metabolically active and may be responsive to systemic stimuli, as well as a potential mediator of inflammation in joint tissue.

As with SAT and VAT, the IFP may also become increasingly dysfunctional in individuals with OA and obesity. Macrophages were found to permanently reside within the IFP and exhibit M1-like and M2-like polarization states when exposed to bioactive molecules [225]. Accordingly, in patients with obesity and OA, the inflammatory profile of IFP was shown to change with variations in immune cell abundance [226–229]. Harasymowicz et al. [226] found that compared to lean individuals, those with both obesity and OA had an increased abundance of CD45+, CD45 + CD14+, and CD14 + CD206 + macrophages in the IFP. Additionally, two other studies found that in the IFP of patients with OA, there was a greater proportion of macrophages presenting cell surface markers associated with anti-inflammatory M2-like macrophages (CD206 and CD163) than pro-inflammatory M1-like macrophages [227–230]. However, the latter studies and others [225, 227, 230] did not find that BMI influenced the proportion of infiltrating macrophages in the IFP and surrounding tissue, suggesting that obesity itself may not directly affect macrophage abundance but rather the phenotypes of these immune cells. The IFP contains various populations of macrophages, although the mechanisms underlying macrophage infiltration in the IFP, as well as their specific functions with regard to OA pathogenesis, remain to be elucidated.

Overall, the physiology of the IFP may impact the progression of OA in individuals with obesity. However, whether adipocyte- and macrophage-derived soluble factors, macrophage infiltration, or cellular changes within the IFP contribute to the initiation and progression of OA is unclear because most studies examined IFP samples harvested from patients with end-stage OA during knee replacement surgery. At this late stage of the disease, the IFP was usually found to contain more anti-inflammatory macrophages (CD206 + or CD163 + cells), hypertrophied adipocytes, fibrotic lesions, and increased concentrations of inflammatory signals [215]. Future research may want to further characterize the IFP during earlier stages of OA to understand more clearly whether these characteristics are unique to the IFP and to fully grasp the contribution of these cellular changes in OA pathogenesis.

7 | Cancer

Adipose tissue inflammation may contribute to carcinogenesis via multiple mechanisms, including the dysregulation of adipokine and cytokine secretion, enhanced immune cell responses, and increased production of certain hormones. To examine the contribution of AT inflammation in carcinogenesis, most studies have focused on AT depots adjacent to cancerous cells. However, AT inflammation in other depots may also contribute to the occurrence of cancer. While obesity is associated with more than 13 different types of cancers [231, 232], this review will focus on breast and colorectal cancers because they are the most prevalent cancers in men and women with obesity [233, 234].

7.1 | Breast Cancer

7.1.1 | Cellular Characteristics of Adipose Tissue in Breast Cancer

Changes in the breast AT microenvironment can influence the development of pathological conditions in breast tissue. The presence of crown-like structures is a hallmark feature of AT inflammation in various depots including breast AT and is associated with a higher risk of breast cancer, poor prognosis and progression toward metastatic disease [50, 51, 76, 235–238]. Patients with breast cancer and obesity had about three to seven times higher odds ratio for crown-like structures in breast tissue compared to patients with breast cancer who were normal weight [50]. Furthermore, crown-like structures were more abundant and contained more M2-like macrophages in breast AT adjacent to the tumors when compared to healthy breast tissue [75, 78]. Although M2-like macrophages are typically known to have anti-inflammatory properties, their immunosuppressive role may promote tumor development and progression [240]. In addition, obesity may also alter breast ATM function, causing them to adopt a metabolically activated pro-inflammatory phenotype, which may promote tumorigenesis [108]. An *in vitro* study demonstrated that the secretory factors extracted from obese VAT macrophages

promoted lipid accumulation and expression of inflammatory markers in human breast cancer cells when compared to monocyte-derived macrophages [241].

BMI increments and indices of central obesity have been shown to be positively associated with breast adipocyte size independent of age, and menapausal status [52, 53]. Breast adipocyte size was also found to be positively associated with breast cancer grade, stage, and prognosis [50, 52, 54]. For instance, Almekinders et al. [54], found that large breast adipocyte size was significantly associated with an increased risk of invasive ductal carcinoma regardless of the stage and receptor status. Among other markers of AT dysfucntion, AT fibrosis may also contribute to the development of breast cancer as increased mammographic breast density is an independent risk factor for breast cancer [242–244]. Obesity promotes mammary gland fibrosis by increasing the recruitment of fibrocytes, collagen biosynthesis, and ECM remodeling, which may increase the risk of breast cancer [245, 246]. In fact, several *in vitro* studies showed that obesity triggered ECM remodeling and increased breast cancer cell growth, invasion, and metastasis [247–253].

7.1.2 | Contribution of Regional Adiposity Toward Breast Cancer Progression

The impact of regional adiposity among breast cancer patients has been investigated through numerous retrospective studies. Central adiposity, particularly increased VAT, emerges as a critical determinant associated with poor prognosis among breast cancer patients when compared to other AT depots. Increased waist circumference and waist-to-hip ratio (WHR) were associated with increased all-cause mortality and increased breast cancer–specific mortality [254]. A *U*-shaped relationship was also observed where low and high BMIs and WHRs were associated with an increased mortality rate among patients with breast cancer [255]. Moreover, increased VAT and decreased VAT/SAT ratio were associated with worsened outcomes, poor survival rates, and increased recurrence rates in breast cancer patients [256–259]. Greater VAT mass and VAT containing more lipid were associated with poor survival outcomes in patients with breast cancer [260]. Aside from VAT, increased SAT volume was also associated with an increased risk of death in patients with non-metastatic breast cancer [258]. However, depending on the region, SAT appears to have different effects on breast cancer. Increased abdominal and low gluteofemoral SAT volume has been associated with increased recurrence and poor survival rates [261]. More studies should investigate the potentially protective role of gluteofemoral SAT in breast cancer.

Tumor stage, histological type, and receptor status may also be associated with regional adiposity. Stages 3 and 4 cancers, human epidermal growth factor receptor 2 positive (HER-2+), and triple-negative breast cancers had the highest hazard ratios for mortality and poor survival rates [255–257, 259–261]. Only a few studies examined these factors in relation to adiposity, and the findings remain inconclusive. Zhang et al. [255] reported that the association between BMI and all-cause mortality in breast cancer patients is consistent regardless of estrogen receptor status, tumor stage, or menopausal status [255]. The *U*-shaped relationship between WHR and mortality was marginally decreased in estrogen receptor positive patients. However, researchers speculate that this could be due to endocrine therapies, such as tamoxifen, that improves the outcomes in estrogen receptor–positive patients [255]. In contrast, another study observed that stage 3 and 4 breast cancers and estrogen receptor positivity significantly increased the negative associations between abdominal and gluteofemoral SAT volumes with survival rates [261]. No significant effects were observed by progesterone receptor or triple-negative tumor status [261]. While the evidence is limited, tumor stage and estrogen receptor status may influence the impact of obesity on breast cancer risk and survival.

7.1.3 | The Role of Adipokines and Cytokines in Breast Cancer

AT inflammation may also increase breast cancer risk via the dysregulation of adipokine and cytokine secretion. Greater leptin and low adiponectin concentrations have been associated with increased breast cancer risk even after the adjustments for obesity indices [262–266]. While most studies observed no significant differences in leptin and adiponectin levels in either estrogen, progesterone, or HER2 positive or negative breast cancer patients [262–265], Kang et al. [266] observed significantly higher adiponectin levels in estrogen receptor–positive patients [266]. Adiponectin has antiproliferative and proapoptotic effects on breast cancer cells. Recombinant adiponectin increased the expression of proapoptotic genes and inhibited the cell cycle in triple-negative breast cancer cells (MDA-MB 231) [267] and estrogen and progesterone receptor–positive breast cancer cells (MCF-7) [268]. Adiponectin is found in lower concentrations among those with obesity, especially in postmenopausal women, corresponding with a greater risk of breast cancer in this demographic [270–272]. On the other hand, leptin has been found to promote the proliferation, migration, and invasion of breast cancer cells by increasing various signaling pathways [273, 274]. Leptin promoted the epithelial–mesenchymal transition via upregulation of pyruvate kinase M2 expression and activation of PI3K/AKT signaling pathway, thereby promoting breast cancer growth and metastasis [273]. These findings were observed across multiple breast cancer cell lines, including estrogen receptor positive, progesterone receptor positive, HER2 positive, and triple-negative cell lines. With obesity, the accumulation of AT increases leptin secretion, resulting in a poorer breast cancer prognosis.

Among the inflammatory cytokines associated with obesity, TNF-α and IL-6 are the most studied for their tumorigenic properties in breast cancer development [274–276]. High TNF-α and IL-6 levels are strongly associated with increased breast cancer risk in women with central adiposity [277, 278]. TNF-α is thought to promote breast cancer by sustaining tumor cell proliferation and stimulating breast cancer cell invasion and metastasis [279]. AT-derived IL-6 has also been found to promote breast cancer metastasis via upregulation of several cell signaling pathways [274, 280, 281, 284]. In addition, IL-6 may expand cancer stem cell populations in ductal carcinoma

in situ [284] and HER2 positive cancer cells [284]. However, some clinical studies have shown contradictory findings observing either positive associations or nonsignificant associations between TNF-α, IL-6, and breast cancer [285–287]. These differences may partly arise because of the variations in the breast cancer cell phenotypes. An *in vitro* study found that TNF-α had different effects on cell proliferation, cell signaling pathways, and cell cycle progression on three breast cancer cell phenotypes [276]. For example, TNF-α increased cancer cell apoptosis and reduced cell cycle progression on MDA-MB-231 (triple-negative) breast cancer cells, while cell proliferation and cell signaling pathways were increased in SK-BR-3(HER + ve) breast cancer cells [276]. Similarly, IL-6 also exhibited varying anti-adhesive and growth-inhibitory effects on different breast cancer cell lines [288–290].

Locally secreted factors may also be crucial in the development of breast cancer in obesity because of the direct effects on the tumor microenvironment. However, limited studies have investigated the local expression of adipocytokines and their receptors in relation to BMI. For instance, the expression of leptin was higher in the tumor microenvironment of patients with obesity when compared to overweight and normal-weight patients [291]. Conversely, another study observed no statistically significant difference in either leptin, leptin receptor (ObR), adiponectin, or adiponectin receptor (AdipoR) between patients with ductal carcinoma in situ or invasive breast cancer across BMI categories [292]. To date, no studies have directly compared the expression of adipocytokines in breast AT to other AT depots.

7.1.4 | Other Obesity-Associated Factors Increasing Breast Cancer Risk

Adipose tissue inflammation may also further potentiate the development of breast cancer in postmenopausal women with obesity by increasing the circulating levels of estrogen, especially in estrogen-dependent breast cancer [293–296]. In postmenopausal women who developed breast cancer, those with obesity had 35% higher circulating concentrations of estrone and 130% higher concentrations of estradiol when compared with lean women [296]. Moreover, increased BMI and higher levels of an estrogen metabolite (16α-hydroxy estrone) were individually and jointly associated with increased breast cancer risk when compared to postmenopausal women with low BMI and low circulating estrogen metabolite levels [297]. The increased estrogen production in obesity may be the result of greater aromatase activity and aromatase mRNA expression in AT [51, 298]. Furthermore, leptin and IL-6 appear to also facilitate the increase in aromatase activity by influencing several cellular signaling mechanisms such as NF-κB pathway and increased prostaglandin E2 production [51, 299, 300].

The effects of obesity-associated AT inflammation is often underexplored as most studies focus on genetic and hormonal factors because of their well-established roles in breast cancer development. However, the effects of nongenetic factors such as higher BMI, increased physical activity, and low alcohol intake have been shown to reduce breast cancer risk even in genetically predisposed women [301]. Therefore, more integrative research approaches are required to understand the multifactorial nature of the disease.

7.2 | Colorectal Cancer

7.2.1 | Local Adipose Tissue Inflammation in Colorectal Cancer

The association between obesity and colorectal cancers is well established [302–305], and early-life obesity carries a greater risk of developing colorectal cancer [306–308]. Studies showed that the inflammation of the peritumoral VAT is highly associated with colorectal cancers [309–312], and this association is stronger in patients with obesity [312]. One of the changes that occurs in peritumoral VAT is adipocyte transformation into cancer-associated adipocytes where the surrounding adipocytes adopt a different phenotype, which promotes colorectal cancer progression [313, 314]. The cross-talk between the cancer cells and the adipocytes creates an ideal tumor microenvironment by altering immune cell infiltration, secretion of adipokines and cytokines, and expression of adhesion molecules [313–316].

Peritumoral VAT has been found to be infiltrated with M2-like macrophages, which have protumorigenic effects in colorectal cancer [310, 311]. Zoico et al. compared peritumoral VAT, VAT, and SAT obtained from 20 male patients with colorectal cancer and observed that peritumoral VAT was predominantly infiltrated by a CD68+/CD163+/IDO- M2–like macrophage subset when compared to other depots [310]. On the other hand, murine studies demonstrated that M1 macrophages may be protective against tumor local invasion and peritoneal seeding by enhanced tumor phagocytosis, promotion of cytotoxic T-cell recruitment and activation, and increased cancer stem cell apoptosis [317, 318]. As obesity is characterized by an increased infiltration of M1-like macrophages in VAT [319], obesity should be protective against colorectal cancer. However, such protective effects are not observed clinically. The differential macrophage polarization in the peritumoral VAT in patients with colorectal cancer may arise from the unique tumor microenvironment created by cancer cells and AT. An *in vitro* study observed that colorectal cancer cells secreted factors that resulted in a mixed population of M1/M2 ATM phenotypes, suggesting that tumor-secreted factors alone cannot facilitate the polarization of macrophages [320]. Thus, additional factors, such as adipokines, present in AT are likely important in ATM polarization [316]. However, the limited evidence precludes definitive conclusions on the role played by peritumoral VAT macrophages in colorectal cancer.

In addition, peritumoral VAT also has an increased expression of pro-inflammatory cytokines (IL-6, TNF-α, and angiogenic factors) [309, 311, 312] and increased expression of the number of receptors and adhesion molecules [309, 321] in patients with colorectal cancer. The expression of such markers may promote cancer cell invasion and metastasis and was further increased in patients with colorectal cancer who had obesity compared to those who were lean [312]. Furthermore, peritumoral VAT also exhibit increased expression of adiponectin [310, 312]. Although adiponectin is typically known for having anti-inflammatory

properties, adiponectin also plays a role in tissue repair and cell regeneration that may promote tumor progression [322].

7.2.2 | Systemic Markers of Adipose Tissue Inflammation on Colorectal Cancer

Several studies found significant associations between AT-derived cytokines and adipokines in colorectal cancer [312, 323, 324]. Pro-inflammatory cytokines including TNF-α, IL-6, and IL-8 were positively associated with colorectal cancer [312, 324, 325], and these associations were strongest in colorectal cancer patients with obesity compared to healthy control and lean patients with colorectal cancer [312]. Greater serum levels of IL-6 and TNF-α were also associated with greater BMI in patients with colorectal adenomas [324]. Similarly, TNF-α receptor–lacking mice had reduced infiltration of immune cells and mucosal damage, thereby attenuating colorectal carcinogenesis following ingestion of inflammation-inducing agents [326]. IL-6 may induce tumorigenesis by promoting M2-like macrophage polarization in the tumor microenvironment [327]. IL-6 also activates the signal transducer and activator of transcription factor 3 (STAT3) pathway in the gut mucosa, which ultimately promotes tumorigenesis and cancer development [328].

Many studies observed a negative correlation between serum adiponectin levels and colorectal cancer risk [329–333]; this association was stronger in men than in women [329, 330]. However, although adiponectin is generally considered protective to metabolic disease, a recent meta-analysis revealed that elevated adiponectin levels in overweight individuals were linked to an increased risk of colorectal cancer [329]. The same study showed that high adiponectin levels were only protective in lean individuals where greater adiponectin was associated with a decreased risk in colorectal cancer [329]. Thus, further investigations are required to understand the different effects of adiponectin on colorectal cancer in the context of adiposity and sex.

Human colorectal cancer cells have been found to express adiponectin receptors [322, 331], and *in vitro*, adiponectin inhibited the growth of colorectal cancer via the activation of the AMP-activated protein kinase pathway [332]. As such, even though colorectal cancers express adiponectin receptors, low adiponectin levels in obesity may be insufficient to elicit protective effects. The stage of colorectal cancer may also play a role in the tumor response to adiponectin. In the more advanced stages of colorectal cancer, the expression of the adiponectin receptor was at its lowest indicating that regardless of adiponectin concentrations, the response of cells to adiponectin is limited [322].

Circulatory levels of leptin were positively associated with increased colorectal cancer risk [330, 333–336]. Although this association was stronger in males [330, 336], a few studies done on females showed that leptin was an independent risk factor for colorectal cancer in women regardless of BMI, age, and other known risk factors [333, 334]. In mice with obesity, leptin promoted tumorigenesis via the increased proliferation of colonic epithelial and cancer cells [337–339]. Furthermore, mice with colorectal cancer exhibited a marked increase in leptin receptor expression, whereas in leptin receptor–deficient mice, tumor growth was reduced [337]. Overexpression of leptin receptors has also been found in human colorectal tumors [340]. As such, higher leptin levels may in part underlie the development of colorectal cancer in humans.

Although leptin and adiponectin have been independently implicated in colorectal adenoma, interactive opposing effects have been observed; high adiponectin appears to interfere with the tumorigenic effects of leptin and vice versa [330]. As obesity is associated with low adiponectin and high leptin levels, a tumorigenic environment is likely dominant.

7.2.3 | VAT and SAT Inflammation and Colorectal Cancer

Aside from peritumoral VAT, other VAT depots may also impact the occurence of colorectal cancer in obesity [341–344]. Visceral adipose tissue area was positively associated with the presence of colorectal adenomas and was a better obesity index for colorectal adenomas in both sexes when compared to BMI [342]. In patients with colorectal adenomas, multiple and advanced colorectal adenomas were associated with higher VAT areas than solitary non–advanced colorectal adenomas [342]. Indicators of AT inflammation such as pro-inflammatory immune cell infiltration [345], cytokine expression, and adhesion molecule expression were higher in VAT when compared to SAT in patients with colorectal cancer [346, 347]. A study done on 131 patients with colorectal cancer found that the presence of metabolically activated M1-like ATM in VAT was significantly associated with distant metastasis [345].

Although the relationship between SAT and colorectal cancer is poorly documented, SAT may play a protective role in colorectal cancer [348, 349]. However, poor-quality SAT may increase the risk of colorectal cancer. For instance, increased SAT density was associated with increased risk of mortality in patients with colorectal cancer [350]. In 250 patients with colorectal cancer, the total SAT volume-to-density ratio was an independent prognostic factor for survival in patients with metastatic colorectal cancer [348], and higher SAT volume correlated with longer survival in patients with colorectal cancer [348, 349]. Another study observed that in patients with colorectal cancer, gene expression of CD68 and CD163 (M2-like) macrophage markers were positively correlated with BMI in SAT but not in VAT [346]. These findings suggest that SAT depot may play a protective role in colorectal cancer. However, AT dysfunction, as seen in obesity, may elicit counterprotective effects on colorectal cancer [319]. Thus, more research is needed to further understand the mechanisms by which AT inflammation contributes to colorectal cancer.

8 | Cognition, Dementia, and Alzheimer's Disease

8.1 | Excess Adiposity and Cognition

There is increasing evidence suggesting that obesity is an independent risk factor for dementia and Alzheimer's disease even after the adjustments for confounding factors such as APOE ε4 gene, sex, T2DM, smoking, hypertension, education level, or marital status [351, 352]. Excess adiposity may impact cognition by altering brain morphology via gray matter degeneration. Interestingly,

obesity-induced gray matter degeneration was shown to be similar to what is observed in patients with Alzheimer's disease [353]. Several studies indicate that increasing BMI is associated with smaller total brain volume, gray matter volume, hippocampal volume, and reduced gray matter density [353–356]. In addition, increased WC/WHR is related to an increased risk of lacunar infarcts and white matter hyperintensity [354]. Some other structural changes include reduced myelin, altered water and iron content in the white matter [357, 358], and cortical thinning, particularly in the areas that are involved in memory and cognition [355, 358, 359]. Although the exact mechanisms are unclear, obesity-associated inflammation originating in AT may potentially lead to neuroinflammation and neuronal loss [360, 361].

Adipose tissue depots of various anatomical locations may differentially affect brain degeneration and cognition because of their different metabolic and inflammatory characteristics [362–365]. For example, Widya et al. [364] found that in older adults, increased VAT rather than SAT volume was linked to significant microstructural brain tissue damage in both gray and white matter. Increased VAT also seemed to be associated with poor cognitive outcomes and an increased risk of dementia when compared to SAT [363, 365–367]. Kim et al. [368] demonstrated that increased VAT metabolism, in the context of glucose uptake, was positively associated with enhanced cerebral amyloid-β load, which is an indicator of dementia [368]. Interestingly, in the aforementioned studies, the associations with VAT persisted even after the adjustments for age, sex, comorbidities, and other confounding factors [363, 364, 368]. However, the effects of SAT appear to be protective and may depend on sex. In women but not men, increased abdominal and thigh SAT volume was associated with a decreased risk of dementia [371]. Furthermore, in mice, SAT transplantation into the visceral compartment restored hippocampal synaptic plasticity and improved chronic obesity, indicating that SAT may be neuroprotective [371]. Further research is needed to understand the effects of adiposity on cognition.

8.2 | Adipokines and Cognition, Dementia, and Alzheimer's Disease

Unlike other organs, the brain is protected by the blood–brain barrier and cerebrospinal fluid, which regulate the brain microenvironment [371]. Thus, when assessing the impact of adipocytokines in dementia and cognition, adipokines and cytokines levels in serum and cerebrospinal fluid, blood–brain barrier permeability, and bioavailability need to be carefully considered. For instance, among the adipocytokines secreted by AT, leptin, TNF-α, and IL-6 pass through the blood–brain barrier via a saturable transport system [372]. However, IL-6 has a shorter half-life in cerebrospinal fluid due to its rapid degradation [372]. Because of its low molecular weight, adiponectin crosses the blood brain barrier through receptor-mediated transcytosis [373].

Leptin plays a protective role on cognition via interactions with the hippocampus and hypothalamus, resulting in improved performance in spatial learning and memory [6]. According to a systemic review and meta-analysis that included 24 cross–sectional and 18 observational studies, lower plasma and cerebrospinal fluid levels of leptin were associated with increased risk of dementia and Alzheimer's disease, whereas higher serum leptin levels were associated with better cognitive function [374]. As such, one would expect the risk of dementia and Alzheimer's disease to be reduced in obesity because greater adiposity results in greater leptin concentrations. However, ncreasing BMI and age significantly weakened the association between leptin and cognitive function [374]. The limited leptin transport into the cerebrospinal fluid via the saturable transport system, and the development of leptin resistance with obesity may explain the absence of protective effects by leptin on cognition in patients with obesity. A few studies demonstrated a higher cerebrospinal fluid/plasma leptin ratio in normal-weight individuals when compared to individuals with obesity, suggesting that leptin transport into the brain may be impaired in those with obesity [375]. The expression of leptin receptor mRNA has also been shown to be decreased in Alzheimer's disease patients, indicating a significant disruption to the leptin signaling pathway [376].

Animal studies observed protective effects of adiponectin against oxidative stress–induced dementia [377, 378]. Adiponectin elicited anti-inflammatory effects in the brain by reducing microglial and astrocyte activation and cytokine modulation [377, 378]. Furthermore, adiponectin deficiency in mice brains led to the inactivation of AMP-activated protein kinase, insulin desensitization, and an Alzheimer's disease–like pathology [379]. However, these results may not translate clinically to humans. A systemic review with meta-analysis that included 24 studies found that in 71% of the included studies, patients with Alzheimer's disease had marginally higher adiponectin circulatory levels when compared to cognitively normal individuals [374]. Furthermore, increased cerebrospinal fluid adiponectin levels were significantly associated with mild cognitive impairment when compared to cognitively normal controls [380]. However, the meta-analysis revealed no significant correlation between adiponectin levels and dementia severity. Confounding factors, such as advanced age, sex, and higher BMI were associated with a weaker correlation and may explain the variability observed across studies [374]. Though, the discrepancies between pre and clinical studies may be due to the suppression of adiponectin receptors caused by obesity-associated inflammation. A murine study observed that a high-fat diet-induced oxidative stress suppressed adiponectin receptor 1 and induced Alzheimer's disease–like pathology in the brains of the mice [381]. Low levels of adiponectin in obesity along with the suppression of adiponectin receptors may dampened the protective effects of adiponectin in individuals with obesity.

Although TNF-α has been widely studied in the context of obesity, dementia, and Alzheimer's disease, clinical studies show contradictory findings. While several studies have found positive associations [382–385] between dementia/Alzheimer's disease and serum levels of TNF-α, others observed negative [386, 387] or no association [388–391]. Similar observations were also made in cerebrospinal fluid [391, 392]. Like adipokines, such differences may also stem from the bioavailability of TNF-α at the tissue level, expression of receptors, and blood–brain barrier permeability. Additionally, TNF-α may have protective and degenerative effects on neurons depending on the type of receptor activated [393, 394]. Upon binding to TNF receptor-1, TNF-α can induce the secretion of enzymes that produce reactive oxygen and nitrogen species, thereby promoting

neuroinflammation. Conversely, activation of TNF receptor-2 is neuroprotective and promotes tissue regeneration [395]. The regulation of these receptors in relation to obesity has not been explored and the differential activation of TNF receptors via the NF-κB pathway may underlie the neurodegenerative effects of TNF-α [396].

The role of IL-6 in dementia and Alzheimer's disease is unclear. Most clinical studies that measured serum and cerebrospinal fluid IL-6 in dementia and Alzheimer's disease patients showed either positive [382–384] or nonsignificant associations [385, 386, 389–391], while only a few showed negative correlations [387, 397]. IL-6 is thought to worsen dementia and Alzheimer's disease by inhibiting neurogenesis, decreasing synaptic plasticity, and disrupting learning and memory processes [394]. In contrast, it was also observed that IL-6 and IL-6 receptor/IL-6 fusion protein prevented neuronal and oligodendrocyte degeneration [398].

Although most of the clinical studies that examined the effects of TNF-α and IL-6 on cognition included both males and females, none specifically assessed the effects of sex as a potential confounding factor. Additionally, no studies reported adjusted results for BMI or adiposity, which may explain the variability observed across the studies. Thus, further research is required to fully understand how these mechanisms are associated with Alzheimer's disease in obesity.

8.3 | Adipose Tissue Macrophages and Cognition, Dementia, and Alzheimer's Disease

To our knowledge, there is limited clinical evidence on the effects of ATM in Alzheimer's disease and dementia. A recent study done on humans observed greater infiltration of pro-inflammatory immune cells including M1-like macrophages into the brains of patients with Alzheimer's disease when compared to the control group [399]. Similarly, in mice, proinflammatory M1-like macrophages were found in the hypothalamus of high-fat diet–fed obese mice, which exhibited similar pro-inflammatory and metabolic markers to ATM [400]. Further investigation revealed that in the obese mice, pro-inflammatory macrophages translocate from VAT and infiltrate the hypothalamus, causing neuroinflammation [400]. Another murine study observed that obesity increased blood–brain barrier permeability promoting macrophage infiltration into the brain matter - a process potentially mediated by IL1β, indicating a role of peripherial inflammation on blood brain barrier permeability [401]. Increased hypothalamic macrophage infiltration has also been shown to increase neuroinflammation through elevating nitric oxide synthase [402]. These findings highlight pathways by which macrophage-mediated inflammation in AT may contribute to neurodegenerative disorders.

9 | Emerging Areas of Interest in Adipose Tissue Inflammation and Obesity-Associated Comorbidities

While AT inflammation is still being explored, recent research has focused on novel areas such as inflammasomes, extracellular vesicles, neuroimmune interactions, and single-cell transcriptomics to understand the underlying mechanisms of obesity-associated comorbidities. Inflammasomes, particularly NLRP3 (nucleotide-binding oligomerization domain–like receptor P3), are intracellular protein receptors activated by metabolic stress and lipotoxicity, which promote the release of pro-inflammatory cytokines like IL-1β and IL-18 [403]. This activation exacerbates systemic IR [403, 404] and vascular inflammation, driving metabolic dysfunction and other comorbidities [405, 406].

Extracellular vesicles such as exosomes and microvesicles secreted by the adipocytes and macrophages serve as carriers of bioactive molecules, including cytokines and microRNAs [407, 408]. These vesicles facilitate long-range signaling amplifying inflammation and disrupting metabolic homeostasis in distant tissues [409]. *In vitro* and rodent studies have shown that extracellular vesicles promote vascular remodeling [410] and increase leukocyte attachment to vascular endothelial cells [411], resulting in CVD in obesity. The cellular cross-talk between AT and target organs via extracellular vesicles may further exacerbate chronic AT inflammation and its adverse effects.

The autonomic nervous system, particularly sympathetic innervation inputs, has been shown to influence immune cell responses directly within AT, modulating inflammation [412]. In rodent models, sympathetic nerve activity may modulate AT inflammation by inhibiting TNF-α gene expression in ATMs [413]. Obesity is associated with dysregulated catecholamine signaling via NF-κB pathway activation, attenuating β-adrenergic signaling in the AT, which impairs lipolysis and exacerbates chronic inflammation [414]. In addition, studies also show that upregulation of the cholinergic anti-inflammatory pathway, which is activated by ATM α7 nicotinic acetylcholine receptors, improves glucose homeostasis and IR in obese mice [415]. Thus, therapeutic interventions targeting neural pathways could be a novel strategy to regulate inflammation and obesity-associated comorbidities.

The application of single-cell transcriptomic has revolutionized the study of AT by providing a granular view of its cellular composition and has uncovered novel subpopulations of immune cells, fibroblasts, and adipocytes that were previously uncharacterized [416]. For example, distinct lipid-associated macrophage subtypes with unique inflammatory profiles have been identified in obese AT [417]. Single-cell RNA sequencing has also revealed dynamic changes in stromal cells and adipocytes, particularly in response to metabolic stress [418]. These insights enable researchers to pinpoint cell-specific contributions to AT inflammation and its systemic effects, paving the way for more precise therapeutic interventions.

10 | Conclusion and Future Prospect

In this review, we provide an overview of the relevance and contribution of obesity-induced AT inflammation in the pathogenesis of related comorbidities, specifically T2D, nonalcoholic fatty liver disease, CVD, OA, certain cancers, and dementia. AT inflammation, mediated by macrophages, cytokines, and adipokines, may have local and systemic consequences on health by disrupting the normal functioning of various tissue beds and organs and whole-body homeostasis. Furthermore, cellular

changes in AT characteristics may aggravate inflammation and thus exacerbate the progression of chronic comorbidities in obesity. Future studies should aim to gain a better understanding of AT biology to unravel the underlying mechanisms by which AT inflammation may contribute to obesity-associated comorbidities. Mitigating AT inflammation and macrophage infiltration may represent potential therapeutic targets in the prevention and treatment of metabolic diseases in obesity.

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Conflicts of Interest

The authors declare no conflicts of interest.

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