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Visceral Adipose Tissue Accumulation and Residual Cardiovascular Risk

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Abstract

Purpose of the Review Low-grade systemic inflammation increases residual cardiovascular risk. The pathogenesis of low-grade systemic inflammation is not well understood.

Recent Findings Visceral adipose tissue accumulates when the subcutaneous adipose tissue can no longer store excess nutrients. Visceral adipose tissue inflammation initially facilitates storage of nutrients but with time become maladaptive and responsible for low-grade systemic inflammation. Control of low-grade systemic inflammation requires reversal of visceral adipose tissue accumulation with intense and sustained aerobic exercise or bariatric surgery. Alternatively, pharmacologic inhibition of the inflammatory signaling pathway may be considered.

Summary Reversal visceral adipose tissue accumulation lowers residual cardiovascular risk.

Keywords Obesity · Visceral adipose tissue · Inflammation · Bariatric surgery · Aerobic exercise

Introduction

Patients with cardiovascular disease (CVD) remain at risk for subsequent CVD events despite intensive secondary prevention therapy [1]. Low-grade systemic inflammation enhances the residual CVD risk of patients who are receiving such therapy [2]. In the current obesity epidemic, accumulation of adipose tissue (AT), particularly visceral adipose tissue (VAT), is a common cause of low-grade systemic inflammation [3••]. Obese middle-aged individuals without hypertension (HTN), hyperlipidemia (HLD), and diabetes are at a much greater risk of CVD events than their lean counterparts [4]. Further, obesity is the only independent determinant of atherosclerosis progression in patients who are receiving guideline directed therapy for HTN and HLD [5]. Thus, obesity begets low-grade systemic inflammation that in turn may heighten CVD risk in patients with preexisting vascular disease.

The present review examines the diverse sites of AT accumulation as the balance between nutrient excess and energy expenditure deteriorates. The review then details the VAT transition from an adaptive to a maladaptive inflammatory state and emphasizes the role of the central nervous system (CNS) and bone marrow derived immune cells (BMDIC) in the pathobiology of VAT accumulation and inflammation (Fig. 1). Lastly, the different therapeutic approaches that aim at reversing VAT accumulation or minimizing the adverse effects of VAT on residual CVD risk are discussed.

Accumulation of Adipose Tissue

Body mass index, the ratio of body weight in kilograms over height in meter squared (BMI, kg/m^2), is routinely used in

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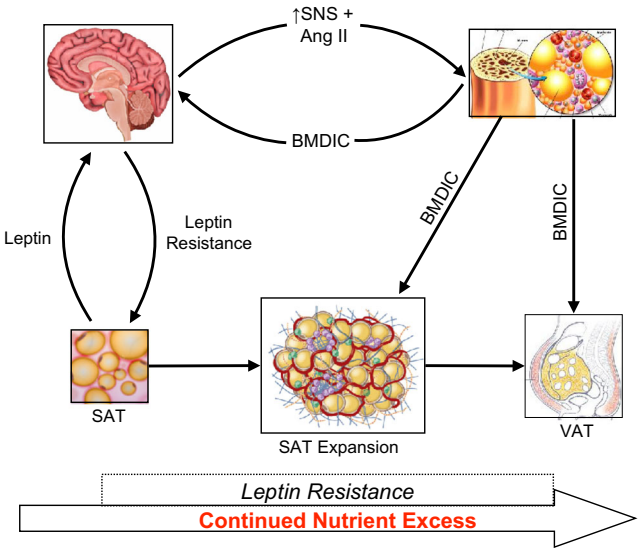

Fig. 1 Nutrient excess leads to neuro-inflammation and production of leptin and angiotensin II (Ang II) by subcutaneous adipose tissue (SAT). Acting on hypothalamic neurons and microglia, leptin and Ang II activate the sympathetic nervous system (SNS) and induce resistance to leptin's anorexic effect through metabolic inflammation (meta-inflammation)-related negative regulatory pathways. Leptin resistance leads to protracted nutrient excess that promotes SAT expansion. Patients tend to accumulate visceral adipose tissue (VAT) when SAT can no longer expand and store nutrients. Increased SNS activity and Ang II levels promote recruitment/engraftment of bone marrow-derived immune cells (BMDIC) in the hypothalamus and VAT. Whether obesity leads to hypothalamic meta-inflammation or hypothalamic meta-inflammation regulates the susceptibility to obesity through leptin resistance remains to be determined

clinical practice to define obesity and reveal the accumulation of AT [6]. Patients with a BMI ≥ 25 and < 30 kg/m^2 are classified as overweight, and those with a BMI ≥ 30 kg/m^2 are classified as obese. In men, AT preferentially accumulates in the trunk and upper body, whereas in women it preferentially accumulates in the hips and thighs [7••, 8]. Lipoprotein lipase activity, the rate-limiting step in AT accumulation from circulating triglycerides (TG), is greater in the abdominal region in men, whereas it is greater in the gluteal than in the abdominal region in women. Sex hormones, principally estrogens, affect regional AT accumulation and enhance the potency of anorexic signals such as leptin, cholecystokinin, and brain-derived neurotrophic factor (BDNF) while reducing the potency of orexigenic factors such as melanin-concentrating hormones and ghrelin [9]. Human AT expresses β 1-3 adrenergic receptors that exert a lipolytic effect and α 2 adrenergic receptors that have an anti-lipolytic effect. Estradiol increases α 2-adrenergic receptor expression in subcutaneous adipose tissue (SAT), but has no effect on intra-abdominal adipocytes [9]. Reversal of the β 1-2/α 2 adrenergic receptor ratio after the menopause promotes accumulation of intra-abdominal SAT and VAT that is associated with production of small low-density lipoprotein particles, thereby increasing CVD risk [10].

Adipose tissue accumulates in three compartments. The subcutaneous AT(SAT) accounts for 80–90% of total AT, whereas VAT and perivascular AT account for 5–15 and 2–3%, respectively [11]. SAT consists of superficial and deep layers. Metabolic and inflammatory genes are preferentially expressed in SAT superficial and deep layers, respectively [12–14]. Deep layers of the SAT undergo greater expansion when obesity develops and correlate more strongly than superficial layers with obesity-related insulin resistance and CVD [13]. Ectopic AT may also accumulate in the heart (myocardial, epicardial, and pericardial layers), liver (hepatic steatosis), pancreas, kidneys (renal sinus fat), and the abdomen (omental, mesenteric, and extraperitoneal) [11].

The term VAT refers to intra-abdominal accumulation of mesenteric and omental AT measured by a single slice CT at the level of L4–L5 or at the umbilicus [15]. Multiple slice imaging by MRI has shown that the amount of VAT varies in different slices [15]. Weight loss and resistance training programs lead to significant changes in the distribution of VAT area from the L3–L4 to the L2–L3 disc level following the interventions [16]. In the absence of intervention, a slice located 5–6 cm above L4–L5 disc provides the most accurate assessment of total VAT [17]. Waist circumference (WC) and waist to hip ratio (WHR) do not quantitatively reflect the amount of VAT [15]. However, an enlarged WC is a convenient qualitative signal of excess VAT in postmenopausal women [18]. Importantly, measurements of WC and WHR are somewhat operator dependent, and thus repeated measurements ideally should be performed by the initial operator [17].

Since only 5–15% of total AT resides in the visceral compartment, the total amount of VAT cannot be estimated from body weight or BMI [19]. The long-established paradigm that VAT accumulates when SAT can no longer expand to store more lipid has been recently challenged by the unexpected lack of correlation between intra-hepatic lipid accumulation and subcutaneous adipocyte size after 8 weeks of excess caloric intake [20–22]. At the population level, VAT accumulation may be inferred from a markedly elevated BMI that intimates near exhaustion of SAT storage capacity for lipid [23–25]. At the clinical level, a third of obese patients do not accumulate VAT and have no or minimal metabolic abnormalities. These patients are classified as metabolically healthy obese (MHO) [26, 27]. MHO appears to be a transitional state, however, as the adipokine profile (adiponectin/leptin/resistin) of MHO postmenopausal women is intermediate between that of normal weight postmenopausal women without and with metabolic abnormalities [28], and one third of MHO patients eventually develop metabolic abnormalities [29]. Further, MHO individuals have a higher risk of CAD, stroke, and heart failure than metabolically healthy normal weight individuals [30••]. In contrast, lean individuals with BMI < 30 kg/m^2 may accumulate VAT and present with obesity-related metabolic

abnormalities and are classified as metabolically obese normal weight persons [31].

Adipocyte hypertrophy mediates VAT expansion, whereas both adipocyte hyperplasia and hypertrophy contribute to SAT expansion in a depot-specific fashion: abdominal SAT expands through adipocyte hypertrophy, and femoral SAT expands through hyperplasia [20]. New adipocytes derived from pre-adipocytes account for 14–20% of cells in SAT [20]. Pre-adipocytes are associated with blood vessels and derive from endothelial cells or pericytes in AT [32]. They differentiate into adipocytes in response to insulin growth factor 1, glucocorticoids, and cyclic AMP [33]. Activation of the transcription factor CCATT enhancer-binding protein-β (C/EBPβ) triggers transcription of peroxisome proliferator-activated receptor-γ (PPARγ) and C/EBPα that activate genes required for the adipocyte phenotype [9, 22, 34, 35].

Pre-adipocytes can undergo senescence with aging and obesity and then release inflammatory cytokines, chemokines, and extracellular matrix proteases [36, 37]. T cell senescence may persist after loss of body weight and mediate chronic inflammation in AT due to continued production of osteopontin [38]. Contrary to conventional wisdom, the total number of adipose cells does not remain constant in adult SAT [39, 40]. However, when obesity develops in childhood or early adolescence, the number of adipocytes remains relatively constant thereafter [40].

Visceral Adipose Tissue

In adults, VAT largely comprises white energy storing adipocytes, with few brown energy dissipating adipocytes [41]. White adipocytes have large uni-locular lipid droplets and minimal uncoupling protein 1 (UCP1), while brown energy dissipating adipocytes have multi-locular lipid droplets and high UCP1 and mitochondrial content. The stromal vascular fraction (SVF) of AT contains immune cells, including resident macrophages which comprise up to 10–15% of AT cell population in lean persons and up to 40–50% in obese persons [42••, 43]. Sex affects VAT accumulation, with women having relatively less VAT and more SAT than men [44]. After controlling for total AT mass, age, and sex hormones, Caucasians have more VAT and less SAT than African-Americans [45–47]. VAT does not appear to be homogeneous: genome-wide arrays have shown that mesenteric pre-adipocytes have a greater capacity for replication and adipogenesis than omental pre-adipocytes [35].

Visceral AT accumulation is associated with a constellation of factors that increase CVD risk, including insulin resistance, hyperinsulinemia, increased small dense LDL and low HDL cholesterol, hypertriglyceridemia, diabetes, hypertension, inflammation, altered fibrinolysis, and endothelial dysfunction [23, 31, 48••, 49]. In contrast, SAT is not associated with metabolic abnormalities, and SAT accumulation does not increase CVD risk independently from BMI [50]. Further, liposuction with surgical removal of abdominal SAT has no effect on CVD risk [51]. After adjustment for general obesity measures (BMI, WC, WHR), only VAT remains associated with markers of systemic inflammation [50, 52]. Increased lipid turnover in VAT and reduced lipid turnover in SAT underlie the association between VAT and metabolic abnormalities [53]. Sympathetic nervous system (SNS) activation enhances inflammation. In men, the SNS is activated in visceral but not in subcutaneous obesity [54, 55]. In women, the SNS is not activated in visceral or subcutaneous obesity [56]. VAT is metabolically highly active and CVD risk correlates with VAT in both obese and metabolically unhealthy lean patients [57–59]. In the majority of obese patients, macrophage infiltration and release of cytokines/chemokines is greater in VAT than in SAT [60, 61]. Persistent blood pressure (BP) elevation, lower BP variability, and incident hypertension have been related to VAT [50, 62, 63]. VAT accumulation in Asian men may account for their increased cardiometabolic risk even in the presence of a normal BMI [31].

Circulating inflammatory markers like CRP and interleukin-6 (IL-6) are poor indices of VAT-related low-grade inflammation: CRP correlates more closely with the amount of SAT than VAT and only 30% of circulating IL-6 originates from AT [64–66]. Further, markers of AT inflammation such as reduction in adiponectin and increase in leptin levels do not reliably assess obesity-related low-level systemic inflammation [67]. Sex hormone binding protein level is inversely related to VAT in premenopausal overweight women [68]. Whether blood levels of classical monocytes reliably reflect $CD11c^{+}$ macrophage infiltration in VAT needs to be confirmed [69].

The link between VAT accumulation and increased cardiometabolic risk remains poorly understood [52]. Although women have less VAT than men, the correlation between VAT accumulation and cardiometabolic risk is much stronger in women than men [19, 70]. Whether VAT accumulation is a manifestation of a general process that leads to metabolic and CVD or whether VAT accumulation plays a direct role in the development of these conditions is debated. A common view is that VAT accumulation signals the body's inability to cope with continuous excessive caloric intake and triggers a downhill course of the obesity syndrome. Proposed specific causes of VAT accumulation such as increased hepatic free fatty acid (FFA) load, activation of the hypothalamic-pituitary adrenal axis and the endocannabinoid system, gonadal steroids, and epigenetic mechanisms have fallen out of favor or await supportive evidence [7••, 71].

Visceral Adipose Tissue Inflammation

As the gap between nutrient overload and reduced energy expenditure widens, unremitting visceral adipocyte hypertrophy leads to hypoxia, exposure to gut antigens, mechanical stress against a rigid extracellular matrix, immune cell infiltration, cytokine and chemokine secretion, and ultimately necrosis and inflammation in VAT [27]. The mechanisms and molecular signaling pathways of metabolic inflammation, i.e., meta-inflammation, have been extensively reviewed over the past decade [72–77, 78••, 79, 80••, 81–85]. The inflammatory responses of VAT and the central nervous system (CNS) to nutrient overload are reviewed here.

Adaptive VAT Inflammatory Response

Initially, the inflammatory response to adipocyte hypertrophy facilitates VAT expansion, remodeling, and lipid storage by stimulating angiogenesis and extracellular matrix degradation [76, 86••]. White adipocytes release FFA into the circulation for oxidation or storage by other cell types. Early in the AT inflammatory response, rapid AT expansion triggers lipid accumulation in and proliferation of resident macrophages [87]. White adipocytes secrete anti-inflammatory adipokines such as adiponectin, fibroblast growth factor-21 (FGF21), and IL-33 that activate innate lymphoid cells (ILC2's) [81, 82]. In turn, IL-33-induced ILC2's generate IL-5 and IL-13 that stimulate release of IL-4 by eosinophils to recruit alternatively activated resident macrophages with a potential for release of norepinephrine and stimulation of β3 adrenergic receptors, leading to activation of beige adipocytes [80, 88]. Norepinephrine may be imported and metabolized by sympathetic neuron-associated macrophages rather than released by AT macrophages [89]. As AT expands, the number of tolerance promoting B cells decreases, as does the number of anti-inflammatory type 1 natural killer T (NKT) cells, invariant (i) NKT cells, T helper 2 (TH2), and regulatory T cells (Tregs) [76, 83, 90]. TH2 cells and Tregs help to maintain macrophages in the alternatively activated state through secretion of IL-4 and Il-10 [83, 90]. Tregs-mediated maintenance of macrophages in the alternatively activated state requires expression of metabolic mediators such as PPAR γ and PPAR δ [77, 83]. Both innate and adaptive immune systems contribute to the inflammatory response to AT expansion [74, 75]. Promoting B cells influence both T cell and macrophage function in VAT [83, 91]. However, suppression of activated B and T cells in obese mice has no discernible effect on macrophage-mediated VAT inflammation [92].

Maladaptive VAT Inflammatory Response

The metabolic alterations associated with nutrient overload interact with immune function as AT expands [92, 93]. Alterations in circulating nutrients and metabolite signals influence macrophage polarization towards the classically activated state through nutrient sensing pathways such as AMPK and mTORC1 [83]. Continued adipocyte hypertrophy leads to adipocyte hypoxia and cell death, with production of pro-inflammatory signals such as monocyte chemotractant protein-1 (MCP1), C-X-C motif chemokine 12 (CXCCL12), retinol binding protein 4 (RBP4), leukotriene B4 (LKB4) colony stimulating factor 1 (Csf-1), and resistin that promote proliferation of classically activated macrophages and macrophage infiltration of white AT [77, 94••, 95, 96, 97••]. Insulin resistance correlates with increasing MCP1 production and thus may trigger inflammation in human VAT [98]. Reduced secretion of IL-10 and increased production of TNF-α and interferon (IFN) γ by iNKT cells also contribute to proliferation of classically activated macrophages that in turn release IL-6 and IL-1β [97••, 98]. Upregulation of major histocompatibility complex class II (MHCII) genes and leptin promote the T helper type 1 (Th1) phenotype [77]. T cells, Th1 cells, and macrophages form crown-like structures (CLS) that phagocytose dead adipocytes. B cells produce antibodies and activate T cells that in turn stimulate Th1 and effector T cells to release the pro-inflammatory cytokines TNF-α and IL-1β [77, 81, 82]. The receptor- and non-receptor-mediated triggers of AT inflammatory responses to nutrient overload/expansion are summarized in Fig. 2.

The two-tier classification of macrophages (classical M1 and alternatively activated M2) observed in high-fat diet (HFD) murine models of obesity may not reflect the human condition where macrophages display a number of phenotypes according the metabolic environment [80••, 93]. Confronted with continuous nutrient overload, macrophages polarize towards the M1 state and activate a lysosomal program of lipid metabolism [93, 94••]. Inhibition of lysosomal function increases lipid accumulation in macrophages and reduces AT release of non-esterified fatty acids (FA) [79, 80••]. In AT with large adipocytes, macrophages play a major role in lipid catabolism [94••]. The role of macrophages in AT inflammation was first described in HFD murine models of obesity that contained abundant CLS around dying adipocytes [84]. However, human obesity is associated with fewer CLS, and macrophages play a lesser role in the adipocyte inflammatory response to nutrient overload/expansion in humans [84]. T cells rather than macrophages predominate in the inflammatory response of human AT to nutrient overload/expansion [107••, 108].

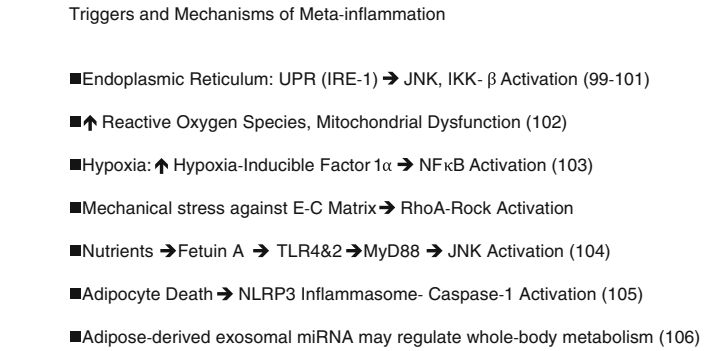

Fig. 2 Unfolded proteins, excess nutrients, and hypoxia result in endoplasmic reticulum (ER) stress. ER stress activates a complex response, i.e., the unfolded protein response (UPR) that contributes to meta-inflammation by activating the inhibitor of κB kinase–β (IKK-β) through the inositol-requiring enzyme 1 (IRE-1) pathway. Increased adipose tissue oxidative stress, obesity-associated mitochondrial dysfunction (due to altered Ca^{++} signaling), and UPR are linked since ER malfunctions or oxidative stress can lead to mitochondrial dysfunction and vice versa. Hypoxia develops in adipose tissue where increasing levels of hypoxia-inducible factor-1α lead to nuclear factor-κB (NFκB) activation. Nutrients (saturated fatty acids) can indirectly activate pattern recognition receptors such as Toll-like receptors (TLR2 &4) that activate Jun N-terminal kinase (JNK) through myeloid differentiation factor 88 (MyD88) signaling. After adipocyte death, pathogen or danger-associated molecular patterns (PAMPs, DAMPs) and homeostasis-associated processes (HAMPs) activate an intracellular multi-protein signaling complex with nucleotide-binding leucin-rich repeat containing receptor 3 (NLRP3 inflamasome) that leads to activation of caspase-1.and secretion of pro-inflammatory IL-1β. Lastly, adipose-derived circulating miRNAs were recently shown to have systemic metabolic effects

Neuro-inflammation

The hypothalamus contains several nuclei that control energy balance through two sets of leptin-sensitive neurons that have opposing actions [109–111]. The first consists of neuropeptide Y (NPY) and agouti-elated peptide (AgRP) neurons. Their activation stimulates caloric intake and reduces energy expenditure through the paracrine action of NPY and AgRP that decreases neuronal activity via GABAergic signaling [112]. The second set comprises proopiomelanocortin (POMC) and cocaine and amphetamine-related transcript (CART) neurons [109]. Activation of POMC/CART neurons decreases caloric intake and increases energy expenditure through release of α- melanocyte stimulating hormone that regulates caloric intake and activates melanocortin receptor-4 in the paraventricular nucleus [109, 113, 114]. Synaptic plasticity and neurogenesis affect the connectivity of AgRP/NPY and POMC/CART neurons [109].

Both neuronal sets have the long signaling form of the long form of the leptin receptor (LEPRb) [115, 116]. Increased leptin levels inhibit AgRP/NPY neurons and activate POMC/CART neurons [109, 116]. Obese patients develop leptin resistance as evidenced by persistence of high caloric intake despite obesity [117–119]. Importantly, nutrient overload may promote leptin resistance in the absence of obesity, and leptin resistance only targets energy homeostasis in obese individuals. Obesity does not affect leptin-mediated SNS activation or CNS upregulation [120–123]. Leptin resistance appears to be related to hypothalamic neuronal inflammation that develops within days of high FFA intake and persists with continued high FFA intake as neuronal inflammation spreads to glial cells [124, 125••, 126–131]. Hypothalamic and VAT inflammation share common signaling pathways that include Iκβ kinase-β/nuclear factor-κβ signaling, c-Jun-N-terminal kinase signaling, Toll-like receptor 4 signaling, endoplasmic reticulum stress, autophagy, and negative regulators such as suppressor of cytokine signaling 3 and protein tyrosine phosphatase 1B [128, 132, 133]. Hypothalamic inflammation affects the progression of obesity through leptin resistance. However, the time course and progression of the hypothalamic and VAT inflammatory response to nutrient overload are not directly related.

Over-nutrition may also mediate leptin resistance by altering the blood-brain barrier [134]. Hyperglycemia disassembles the specialized glial cells (tanycytes) that comprise the blood-cerebrospinal fluid barrier, thereby limiting leptin ingress into the hypothalamus [119]. Nutrient overload-induced neuro-inflammation [132, 135, 136] has also been noted in the hippocampus, cerebellum, amygdala, and brainstem of mice fed a HFD [136].

In HFD-induced murine models of obesity, microglial hypothalamic meta-inflammation regulates energy homeostasis [131]. Whether obesity leads to hypothalamic meta-inflammation or hypothalamic meta-inflammation regulates susceptibility to obesity through leptin resistance in humans is under active investigation [112].

Circulating Immune Cells

Obesity-associated sympathetic excitation bolsters bone marrow production of inflammatory cells that, attracted by local chemokines, infiltrate the CNS and VAT where they differentiate into macrophages [132, 136, 137]. Angiotensin II increases proliferation and differentiation of hematopoietic stem cells while decreasing their tissue engraftment [138, 139]. The spleen serves for storage and rapid deployment of bone marrow-derived immune cells [140]. The crosstalk between CNS, SAT, VAT, and bone marrow is outlined in Fig. 1. Prevention/reversal of VAT accumulation is a rational and direct approach to reducing low-grade systemic inflammation-related CVD risk.

Bariatric Surgery, Inflammation, and Cardiovascular Risk

Roux-en-Y Gastric Bypass (RYGB) Surgery

RYGB surgery consistently reduces circulating levels of CRP, IL-6, and IL-13 levels, while TNF-α levels are unaffected [141–143]. In a study of 65 morbidly obese patients, RYGB surgery decreased pro-inflammatory cytokines, including IL-18, soluble TNF-α receptor 2 (sTNFR2), and CRP in conjunction with a reduction in BMI from 49.2 to 31.9 kg/m^2 [144]. Plasma concentrations of heat shock protein 60 (hsp60), an inflammatory and stress signaling protein, were reported to be lower 6–12 months after RYGB in a study of 53 obese women [145]. In addition to the decrease in circulating inflammatory mediators, RYGB surgery remodels body distribution of AT: 12 months after surgery, the reduction in VAT is relatively greater than that in SAT [146, 147]. VAT but not body weight continues to decrease after 12 months post-surgery [148]. Bariatric surgery reduces subcutaneous adipocyte size and LEPRb expression, but does not decrease adipocyte number [149]. Overall, bariatric surgery is associated with less weight loss in elderly male and diabetic patients [150, 151].

RYGB surgery is associated with a high remission rate of type II diabetes and reduces 10-year CVD risk by 40–50% in obese persons [152, 153]. However, observational studies and meta-analyses have shown that despite a low 10-year CVD risk, obese patients have a high lifetime CVD risk [151, 154–157]. Case-controlled studies with 10–12 year follow-up have shown that bariatric surgery (mostly RYGB) reduces fatal CVD outcomes in obese patients [158, 159••, 160]. In 418 obese patients who underwent RYGB and were followed for 12 years, remission of type 2 diabetes was 75% at 2 years, 62% at 6 years, and 51% at 12 years [158]. The Swedish Obese Subjects (SOS) study reported significant reductions in CV death, myocardial infarction, and stroke in 2010 obese patients who underwent bariatric surgery and were followed for a median duration of 14.7 years [159••]. Further, the Surgical Treatment and Medications Potentially Eradicate Diabetes Efficiently (STAMPEDE) trial demonstrated that 12 months of medical therapy plus bariatric surgery achieved glycemic control in significantly more patients than medical therapy alone [160].

The clear benefits of bariatric surgery on sustained weight loss and remission of type 2 diabetes point to the need for randomized trials of the procedure with mortality as a primary endpoint. Further, the long-term outcomes of bariatric surgical procedures, which are routinely not covered by third party payment, need to be monitored.

Sleeve Gastrectomy

Several lines of evidence point the favorable effects of laparoscopic sleeve gastrectomy (LSG) on low-grade systemic inflammation and VAT. Mean hs-CRP level fell from 8.8 to 2.6 mg/L at 12 months post-LSG in 197 obese patients with a median BMI of 46.8 kg/m^2 [161]. In 110 morbidly obese women, high hs-CRP levels predicted the amount of VAT lost 1 year after LSG [162]. Six to 24 months after LSG, mRNA expression of inflammation-related genes in SAT decreased in 13 obese patients with a mean baseline BMI of 42.3 kg/m^2 [163]. In contrast, mRNA expression of pro-inflammatory cytokines in SAT remained unchanged at 1 and 6–12 months in 17 obese patients with a mean baseline BMI of 46.3 kg/m^2 who underwent RYGB ($n = 7$) or LSG ($n = 10$) [164]. These apparently discordant findings may be related to a predominant effect on of bariatric surgery on VAT rather than SAT in the latter study. The decrease in BMI and relative decrease in CRP levels were similar at 12 months in both studies: 13 versus 12 kg/m^2 and 52 versus 66%, respectively.

Few studies have focused on the effects of LSG on CVD risk, and none has dealt with its effect on VAT. Reduced carotid artery intima-media thickness and increased brachial artery flow-mediated dilation following LSG provide indirect evidence of its beneficial effect on CVD risk [165, 166]. Further, a single-center study comparing LRYGB ($n = 12$) and LSG ($n = 10$) concluded that LRYGB is more effective in resolving low-grade systemic inflammation than is LSG [167]. Recent data indicate that bypass and sleeve gastrectomy have similar effects on weight loss and comorbid conditions through 5 years of follow-up [168]. Longer-term data are needed to ascertain which bariatric procedure is preferred for CVD risk reduction.

Physical Activity and Aerobic Exercise

Present data regarding the effect of physical activity on VAT are inconsistent. In the Framingham third-generation and Omni Ii cohorts, moderate-to-vigorous physical activity (MVPA) measured with accelerometers over a period of 5 days was associated with reduced VAT accumulation [169]. The association between physical activity and VAT reduction was greater in women than in men, and sedentary time was not associated with VAT accumulation [169]. In contrast, MVPA measured with accelerometers over a period of 4 days accounted for only 4% of the variance in VAT in another study of 82 adults with a mean BMI of 30.9 kg/m^2 [170]. A significant inverse association was reported between MVPA and VAT in a study of 271 middle-aged African-American women and men [171]. Overall, vigorous physical activity sustained in time and intensity may lessen VAT accumulation, while sedentary behavior is unrelated to VAT.

Randomized controlled trials of aerobic exercise training clearly indicate a beneficial effect of training for ≥ 8-week duration on VAT accumulation, providing that caloric intake remains constant [172]. Whether sex affects the VAT response to aerobic exercise remains an unresolved issue. Similar decreases in WC were reported in men and women after 12 months of daily aerobic exercise for 60 min/day [173]. Brisk walking for 3 h/week for 12 months decreased intra- and subcutaneous abdominal fat in 168 postmenopausal women with a baseline BMI of 30.5 kg/m^2 [174]. This study showed that VAT accumulation may regress without a concomitant decrease in BMI [174]. A systematic review of 35 studies with a total of 2145 patients showed that aerobic exercise induced VAT reduction but that resistance exercise reduced insulin resistance and lowered LDL cholesterol but did not affect VAT [175]. VAT reduction occurred without significant loss of body weight in 3 of the 35 studies. Aerobic exercise-induced reduction in VAT depends on exercise intensity and duration [176]. Jogging 20 miles/week was shown to decrease VAT by 6.9% compared to 1.7 and 2.5% for walking 12 miles/week and jogging 12 miles/week, respectively [176]. A recent study confirmed the beneficial effects of 80% aerobic and 20% resistance exercise training on VAT. A cohort of 278 overweight/mildly obese women and men who had been previously randomized to a Mediterranean/low-carbohydrate (MED/LC) diet or a low-fat (LF) diet for 6 months were then randomized in factorial 2 × 2 design to 80% aerobic and 20% resistance exercise training three times a week or no training for 12 months [177••]. The MED/LC and LF diets did not affect VAT, while the exercise/resistance training resulted in significant VAT reductions in patients randomized to both diets [177••]. Although weight loss has been reported to have a greater effect on markers of inflammation than aerobic or resistance exercise, present consensus favors diet with physical training over diet without physical training for reduction of obesity-related systemic inflammation [74, 178, 179]. Aerobic exercise decreases low-level systemic inflammation by reducing total AT especially VAT accumulation and by a direct anti-inflammatory effect as evidenced by increased release of IL-1 receptor antagonist and reduced hepatic production of the adaptor protein fetuin-A [180]. Preclinical studies point to the importance of exercise intensity, duration, and frequency for VAT and mitochondrial lipid metabolism remodeling [181]. Finally, moderate caloric restriction for 12 months failed to reduce VAT in the recent Calorie Restriction in Overweight Senior S: Response of Older Adults to Dieting Study (CRSSROADS) [182]. While adherence to a vigorous exercise program appears to be the most effective intervention for VAT reduction, many obese patients are unable to exercise vigorously.

Changes in VAT cannot be estimated from changes in SAT or body weight. Relative percent changes in visceral versus subcutaneous abdominal fat were reviewed in 61 weight loss studies [183]. Save for very-low-calorie diets that resulted in short-term preferential VAT loss, the method of weight loss had no bearing on relative reductions of VAT versus SAT [183]. In contrast, lifestyle modification that includes both healthy eating and aerobic exercise has been associated with preferential loss of VAT in obese and non-obese persons [184–186]. Of note, aerobic exercise for VAT reduction needs to be strenuous with more sessions per week than generally recommended for CVD risk reduction [173, 187].

Obesity is a major barrier to regular aerobic exercise [188]. Fearing negative comments, obese children are reluctant to participate in physical activities [189]. Similarly, obese adults tend to avoid exercise due to embarrassment in gyms and bias from fitness professionals. Morbidly obese patients may only be able to walk short distances, as the metabolic cost of walking on flat ground at moderate speed is close to their anaerobic threshold. Bariatric surgery-induced weight loss is a key step that may break the downward spiral from increase in body weight to steady decrease in physical activity [190].

Pharmacologic Reduction of Systemic Inflammation

The Justification for the Use of Statins in Prevention: an intervention Trial Evaluating Rosuvastatin (JUPITER) reported that lowering systemic inflammation with a statin reduced the incidence of major CVD events in patients with hs-CRP levels ≥ 2 mg/L, LDL cholesterol < 130 mg/dL, and no history of CVD [191]. The reduction in CVD events was twofold greater than that expected from the concomitant reduction in LDL cholesterol. The effect of colchicine, another commonly used anti-inflammatory therapy, on the risk of subsequent CVD events is currently being assessed in two randomized placebo controlled trials [192]. A targeted approach to the reduction of systemic inflammation was used in the Canakinumab Anti-inflammatory Thrombosis Outcome Study (CANTOS) [193]. Ten thousand patients with prior MI and hs-CRP ≥ 2 mg/L were randomized to three doses (50, 150, and 300 mg daily) of canakinumab, a monoclonal IL-1β antibody or to placebo. At a median follow-up of 3.7 years, patients receiving 150 mg of canakinumab experienced a 15% lower risk of major CVD events than patients receiving placebo [193]. Patients with hs-CRP < 2 mg/L while receiving canakinumab experienced a 31% lower risk of major CVD events, whereas patients with hs-CRP ≥ 2 mg/L did not experience any risk reduction [194]. The redundancy of inflammatory signaling pathways may thwart the pharmacological approaches to lessen obesity-related systemic inflammation and metabolic disorders. Canakinumab lowers the risk of CVD events but does not prevent the progression from prediabetes to diabetes [195].

Conclusion

Accumulation of VAT mediates obesity-associated low-grade systemic inflammation and CVD risk. In the absence of specific circulating markers for VAT, BMI is currently used as a surrogate for VAT. Adherence to an intensive aerobic exercise program is requisite for reduction of VAT-associated low-grade systemic inflammation and CVD risk. Bariatric surgery may allow morbidly obese patients with VAT accumulation to undertake intense aerobic exercise. The redundancy of obesity-related inflammatory signaling pathways presents a challenge to development of pharmacologic approaches to inhibiting low-grade systemic inflammation and thus preventing CVD in obese patients.

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Compliance with Ethical Standards

Conflict of Interest The authors declare no conflicts of interest relevant to this manuscript.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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