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Mechanisms through which laparoscopic sleeve gastrectomy mitigates atherosclerosis risk: a focus on visceral adipose tissue

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Abstract

Bariatric surgery is currently considered the key treatment method for patients with obesity and related complications. Among the various surgeries, laparoscopic sleeve gastrectomy (LSG) is the most widely used. Obesity is a multifactor chronic disease characterized by the accumulation of visceral adipose tissue (VAT), leading to susceptibility to cardiac metabolic diseases. Many mechanisms, including abnormal lipid metabolism, insulin resistance, inflammation, endothelial dysfunction, adipocytokine imbalance and inflammasome activation, have been identified as the basis for the relationship between obesity and atherosclerosis. Bariatric surgery, such as LSG, reduces the risk of atherosclerosis in people living with obesity by reducing energy intake, disrupting energy balance and reducing the secretion of intestinal hormones to intervene in these risk factors. This review explores the current understanding of how LSG affects VAT and its impact on the risk of atherosclerosis.

Keywords Obesity, Visceral adipose tissue, Atherosclerosis, Sleeve gastrectomy, CVD

Introduction

Cardiovascular disease (CVD) is the predominant cause of global mortality and encompasses conditions such as coronary heart disease, cerebrovascular disease, and peripheral arterial disease. In 2017 alone, 17.9 million individuals died from cardiovascular disease worldwide, constituting 32% of all global deaths. Of particular significance are heart disease and stroke. Atherosclerosis is a hallmark of coronary artery disease (CAD) and a major contributor to CVD mortality [1]. Atherosclerosis is affected by many risk factors, including dyslipidemia, hypertension, diabetes and obesity.

Obesity, which leads to systemic chronic inflammation, insulin resistance, ectopic fat deposition, and increased blood lipids, has become an important risk factor for a variety of metabolic diseases. The prevalence of obesity has reached alarming proportions globally, driven by unhealthy dietary patterns, excessive caloric intake, and sedentary lifestyles [2]. The increased risk of cardiovascular disease caused by obesity is not only the result of individual weight gain but also affected by body fat distribution. Visceral adipose tissue (VAT), which is different from subcutaneous adipose tissue (SAT), is considered to be more dangerous for fat deposition. An abnormal increase in VAT, a type of adipose tissue, is a risk factor for atherosclerosis [3, 4].

When weight management becomes an important measure for reducing the risk of CVD, we should also

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note that there is a view of the 'obesity paradox'. Studies suggest that a certain degree of overweight can reduce the risk of cardiovascular disease and its related mortality [5]. However, there is evidence that the 'obesity paradox' is based on the maintenance of lean body mass, and to a certain extent, there is a lack of long-term follow-up evidence [6]. At the same time, the 'obesity paradox' exists more in the discussion of chronic heart failure. For atherosclerosis, there is much evidence that it is still associated with VAT content. In any case, a reduction in visceral fat is necessary for reducing the risk of cardiovascular disease and atherosclerosis.

Bariatric surgery is the most effective way to treat obesity in appropriately selected patients [7], as it not only is associated with rapid and significant weight loss in the short term but also reduces obesity-related complications and mortality, which is a unique attribute of various weight loss interventions [8]. In recent years, laparoscopic sleeve gastrectomy (LSG) surgery has become the most widely used bariatric surgery due to its safety, simple surgical technique, and lack of change in the original anatomy of the gastrointestinal tract. LSG has been proven to be an effective method for reducing VAT content and improving atherosclerosis, providing an effective option for rapidly improving cardiovascular health in people living with obesity.

Excessive VAT increases atherosclerosis risk

VAT and atherosclerosis

The global obesity epidemic has been established. Since the 1980 s, the prevalence of obesity in most countries has been on the rise. Obesity is a risk factor for cardiovascular disease, including atherosclerosis, dyslipidemia, type 2 diabetes, hypertension and sleep disorders. Obesity can also lead to the development of cardiovascular disease and cardiovascular disease mortality, independent of other cardiovascular risk factors. The underlying pathology of atherosclerosis is influenced by numerous risk factors, including dyslipidemia, hypertension, diabetes, and obesity. Obesity, in particular, serves as a significant risk factor for atherosclerosis, as it contributes to the development of hyperlipidemia, hypertension, and diabetes—all of which synergistically fuel the progression of atherosclerosis.

The process of atherosclerosis begins in childhood. Macrophage foam cells take up cholesterol esters and deposit in the vascular wall, resulting in thickening of the intima. Further lipid accumulation leads to the development of fat streaks, which seem to be almost ubiquitous in young people [9]. Obesity accelerates these early atherosclerotic changes through a variety of mechanisms, such as insulin resistance and inflammation. According to autopsy studies of children and young adults, obesity and a number of related downstream metabolic cardiovascular risk factors, are associated with the severity of atherosclerotic disease [10, 11].

In a study of the pathological determinants of atherosclerosis in young adults, an association between obesity and increased atherosclerotic lesions in men was found only in people with thicker abdominal fat, suggesting that central obesity plays a fundamental role in the development of atherosclerotic disease [12, 13]. When discussing the cause of abdominal obesity, the role of VAT is considered to be the core. VATs mainly exist in the mesentery and greater omentum and affect the liver through portal vein circulation. Compared with SAT, VAT has more metabolic activity and contains numerous adipocytes, inflammatory cells, immune cells and preadipocytes, and its blood vessels and nerves are also densely distributed. VAT secretes many adipocytokines to promote the occurrence and development of atherosclerosis [14]. In addition, excessive VAT can lead to a hypercoagulable state, and excessive free fatty acids (FFAs) in VAT can also affect vascular endothelial function, which leads to atherosclerosis [4]. Studies indicate that reducing VAT can improve cardiac structure, lower insulin resistance, and consequently decrease the risk of atherosclerosis.

In the next section, we will discuss in detail the specific mechanism of the abnormal increase in VAT as a risk factor for atherosclerosis.

Obesity and atherosclerosis: mechanisms

Hypertriglyceridemia associated with VAT

People with visceral obesity often exhibit an abnormal lipid profile characterized by elevated triglyceride levels and reduced high-density lipoprotein (HDL) levels. This results from both impaired clearance of triglyceride-rich lipoproteins and increased production of triglyceride-rich lipoproteins. VAT, compared to SAT, has more glucocorticoid and androgen receptors, leading to increased production of free fatty acids [4]. These free fatty acids enter the liver through the portal vein, causing the accumulation of fatty acids in the liver and an increase in very-low-density lipoprotein (VLDL) production. Excessive VLDL burdens HDL, and reduced insulin-sensitive lipoprotein lipase (LPL) activity inhibits the hydrolysis of triglycerides in chylomicrons and VLDL, as well as the transfer of lipoproteins between them and HDL, resulting in elevated triglycerides and decreased HDL levels. VLDL and LDL particles in people with visceral obesity are triglyceride-rich, promoting lipid exchange mediated by cholesteryl ester transfer protein (CETP), causing HDL to become triglyceride-rich. Triglyceride-rich HDL is more susceptible to hydrolysis by hepatic lipase, leading to the formation of smaller, more easily degradable HDL3. Consequently, multiple factors contribute to

lower HDL levels in people with visceral obesity. LDL, which is rich in triglycerides, has lower binding efficiency with receptors, increasing its circulation time and susceptibility to oxidative changes within the vascular wall. Moreover, obesity-induced insulin resistance further diminishes LDL receptor expression (15, 16).

Chronic inflammation associated with VAT

Adipose tissue is interspersed with resident immune cells, as are all other solid tissues of the body. In VAT, members of the innate and adaptive immune systems have been identified. These cells include macrophages, dendritic cells, granulocytes, innate lymphoid cells (ILCs and natural killer (NK) cells), and T and B cells [17]. The activation of such immune cells is usually accompanied by local or systemic inflammation of varying intensity. Chronic inflammation leads to an increase in inflammatory cells within VAT and a reduction in the capillarization of adipose cells [18]. Visceral adipose cells secrete a variety of cytokines, among which the functions of leptin, IL-6, adiponectin and resistin are discussed (Insert Fig. 1).

Leptin, a crucial adipokine secreted by adipocytes, primarily regulates energy metabolism and lipid homeostasis through central and peripheral pathways. At the central level, leptin activates the long-form leptin receptor/obese receptor b (OB-Rb) on hypothalamic neurons, suppressing the release of appetite-related neuropeptides (e.g., neuropeptide Y) while stimulating the secretion of catabolism-promoting α-melanocyte-stimulating hormone (α-MSH) [19]. This dual action reduces food intake, and accelerates lipolysis in adipose tissue. Peripherally, leptin directly acts on adipocytes while also modulating vascular tone and suppressing vascular smooth muscle cell proliferation. The study revealed that OB-Rb are expressed in rat vascular smooth muscle cells (VSMCs), and leptin inhibits angiotensin II-induced vasoconstriction through these OB-Rb receptors. This

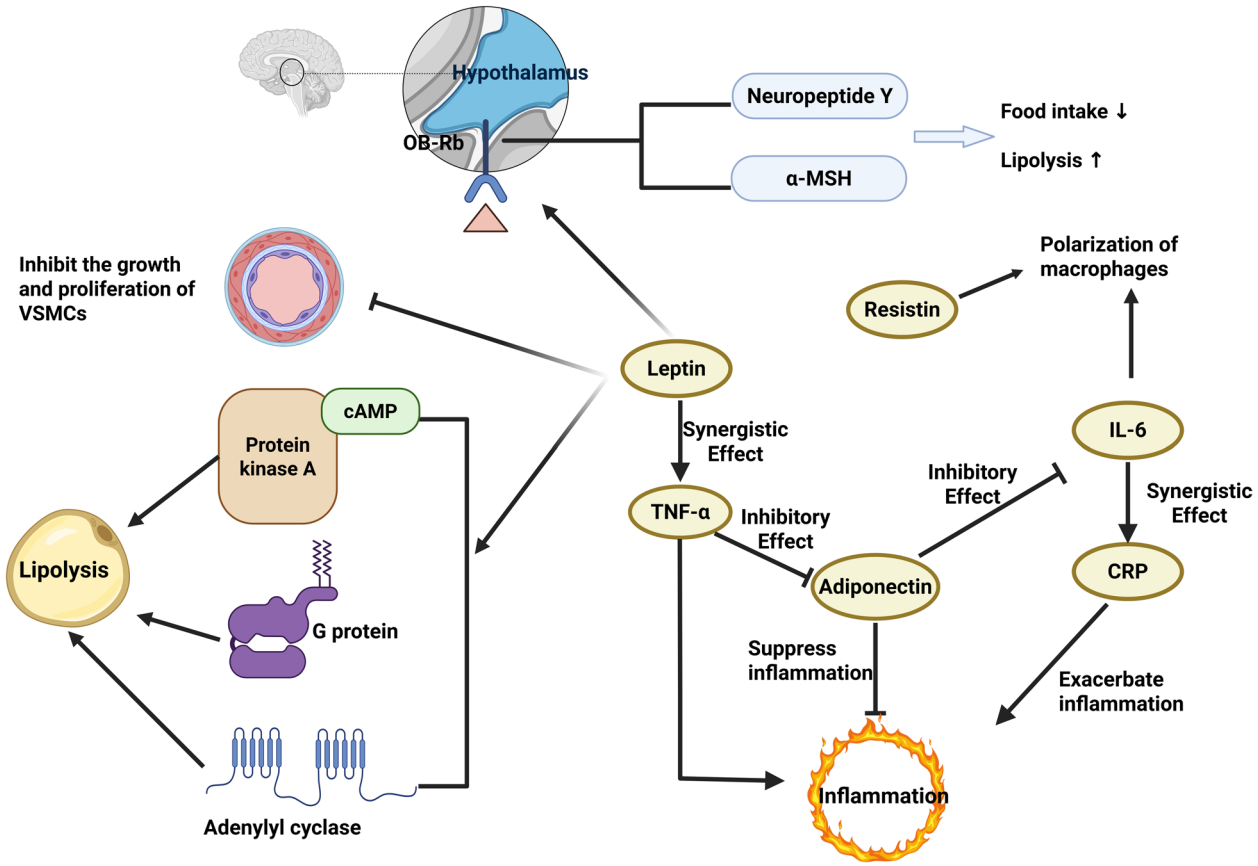

Fig. 1 The dual roles of leptin and other adipokines in metabolic regulation and cardiovascular diseases. Leptin modulates appetite via the hypothalamus and promotes lipolysis, but obesity-induced leptin resistance leads to metabolic dysregulation, triggering vascular inflammation, oxidative stress, and atherosclerosis while activating monocytes/macrophages and stimulating vascular smooth muscle proliferation. IL-6 upregulates CRP to drive inflammatory plaque progression; adiponectin maintains metabolic homeostasis through anti-inflammatory actions; resistin exacerbates metabolic disorders via insulin resistance and pro-atherogenic mechanisms. Visceral adipose tissue secreting pro-inflammatory factors (TNF-α, CRP) creating a vicious cycle of chronic inflammation and vascular dysfunction

mechanism may play a significant role in the physiological regulation of blood pressure [20]. Leptin may inhibit the growth and proliferation of VSMCs, thereby exhibiting protective effects on the cardiovascular system [21]. However, this contrasts with findings from rat experiments, where leptin was shown to significantly stimulate the proliferation of aortic VSMCs in a dose and time dependent manner [22]. As a pleiotropic hormone secreted by adipocytes, leptin promotes lipolysis in white adipose tissue (WAT) through two complementary pathways. First, the NO-dependent pathway [23]: leptin induce nitric oxide synthase (NOS) activity and promote NO production. NO inhibits phosphodiesterase (PDE), thereby reducing cAMP degradation and elevating intracellular cAMP levels, leading to protein kinase A (PKA) activation and enhanced lipase activity. In addition, NO suppresses β-adrenergic receptor signaling through negative feedback and disrupts G protein-coupled pathways, dynamically regulate lipid metabolism. Second, the adenosinergic inhibitory antagonistic pathway [24]: leptin targets the adenylyl cyclase/Gi protein nexus via its receptor, counteracting the sustained suppression of lipolysis induced by endogenous adenosine through the A1 receptor–Gi pathway. This mechanism maintains lipolytic activity by balancing adenosine's inhibitory regulation through homeostatic control.

Leptin exerts complex mechanisms of action on the cardiovascular system. It promotes the development of atherosclerosis through multiple pathways. At physiological concentrations, leptin may enhance endothelial function by promoting NO release and suppressing inflammatory responses, exhibiting potential protective effects. Under pathological conditions (hyperleptinemia), elevated leptin levels activate multiple signaling pathways (e.g., ERK, NF-κB, JAK/STAT), promoting vascular inflammation, oxidative stress, thrombogenesis, and cellular proliferation, thereby accelerating atherosclerosis [25]. Elevated levels of leptin secreted by adipocytes in people living with obesity stimulate human coronary artery endothelial cells (HCAECs) to significantly increase CRP production. This mechanism may contribute to inflammation and thrombogenesis, serving as one of the pathological pathways underlying the heightened cardiovascular risk observed in obese individuals [26, 27]. As a macrophage chemotactic factor, leptin increases the expression of TNF-α, IL-6, and IL-1β in macrophages while also upregulating acetyl-CoA:cholesterol acyltransferase-1 (ACAT-1), leading to cholesterol ester accumulation [26]. In vascular smooth muscle cells, hyperleptinemia may induce"leptin resistance"by downregulating leptin receptor expression, thereby exacerbating vascular dysfunction. Leptin, by increasing matrix metalloproteinase-9 (MMP-9), cyclin D1, and β-catenin expression, mediates the proliferation and migration of vascular smooth muscle cells (VSMCs), thereby accelerating the progression of atherosclerosis [21, 22].

Another crucial inflammatory factor is interleukin-6 (IL-6). IL-6 is an upstream regulatory factor that can control the production of CRP in the liver, playing a central role in the inflammatory response [28]. IL-6 can predict the severity, vulnerability, and progression of carotid artery plaques [29]. As much as 30% of circulating IL-6 comes from adipose tissue, with VAT secreting 2–3 times more IL-6 than SAT [18]. In the early stages of atherosclerotic plaque formation, IL-6 promotes the influx of inflammatory cells. When IL-6 binds to the IL-6 receptor complex, endothelial cells promote the recruitment and migration of white blood cells by increasing ICAM-1 expression [30]. IL-6 also participates in inducing M1/M2b-like polarization of macrophages, promoting vascular intimal hyperplasia [31].

Adiponectin and leptin exhibit diametrically opposite effects on transitions in metabolic status. Elevated adiponectin levels are inversely associated with the risk of progression from metabolically healthy to unhealthy states (e.g., developing metabolic syndrome) in initially healthy individuals while simultaneously increasing the likelihood of regression to metabolic health among those with existing metabolic abnormalities [32]. This association pattern remains consistent across both obese and non-obese populations. The study is the first to reveal that adipokines not only correlate with metabolic states but also directly influence their dynamic evolution: adiponectin promotes metabolic homeostasis through mechanisms such as improving insulin sensitivity and suppressing inflammation, whereas leptin resistance may accelerate metabolic dysregulation [32].

Resistin, which mainly originates from infiltrating macrophages in adipose tissue, is another cytokine secreted by VAT. It induces insulin resistance, leading to metabolic dysfunction [18, 33]. Resistin increases the expression of the adhesion molecules VCAM-1 and MCP-1 in endothelial cells and monocytes, accelerating the adhesion and chemotaxis of endothelial cells and monocytes, factors that contribute to the early formation of atherosclerotic lesions. Resistin also promotes the polarization of macrophages and the formation of foam cells. In addition to its direct impact on atherosclerosis, resistin induces lipid metabolism abnormalities associated with atherosclerosis, promoting the excessive production of apolipoprotein B and VLDL in hepatocytes and resulting in significantly elevated VLDL levels in the blood. This process is regulated by microsomal triglyceride transfer protein (MTP), which increases the transport of lipids in VLDL particles. Moreover, resistin stimulates de novo lipid synthesis in hepatocytes, accelerating the excessive

production of Apolipoprotein B and providing abundant lipid material for atherosclerotic lesions [34].

VAT also secretes other cytokines, such as CRP and TNF-α, which promote vascular inflammatory responses. CRP is a marker of the inflammatory response and may increase macrophage uptake of LDL, which is also believed to be involved in the development of atherosclerosis [35, 36]. Endothelial cells, which are crucial for maintaining vascular homeostasis, are negatively affected by TNF-α, which can decrease NO bioavailability by inducing ROS production and inhibiting eNOS activity, leading to endothelial dysfunction [37]. Tumor necrosis factor-α (TNF-α) also promotes the generation and release of leptin, inhibiting the protective effect of adiponectin on blood vessels. In the process of atherosclerosis, oxidized LDL is recognized by APCs, which induces Th1 and Th17 cells to produce TNF-γ and IL-17, exacerbating the inflammatory response [14].

In addition to promoting the release of proinflammatory factors, VAT also inhibits the release of anti-inflammatory factors. Adiponectin is a classic anti-inflammatory agent that mitigates inflammation by inhibiting macrophage differentiation and promoting the transformation of macrophages to the M2 anti-inflammatory state. There is a negative correlation between visceral fat volume and plasma adiponectin concentration, whereas the situation is different in subcutaneous fat tissue. Adiponectin has multiple protective effects on blood vessels, including exerting anti-inflammatory effects, increasing nitric oxide production, inhibiting endothelial activation, suppressing adhesion molecules (VCAM-1, ICAM-1, and E-selectin), inhibiting foam cell formation, and suppressing smooth muscle migration, proliferation, and plaque stability [38].

Visceral adipose-related insulin resistance

Visceral adipose cells are more prone to insulin resistance than are SAT fat cells [4]. This viewpoint has been confirmed in an IRAS family study, which demonstrated a more significant association between VAT and insulin resistance as well as between VAT and the occurrence of metabolic syndrome (MetS) [39]. The enlargement of adipose cells in VAT leads to a hypoxic environment, accelerating adipose cell death and recruiting more macrophages. Activated M1 macrophages and adipocytes release large amounts of inflammatory factors, exacerbating chronic inflammation and insulin resistance in adipose tissue. Among these factors, TNF-α is a typical representative that is significantly increased in VAT. TNF-α may induce the JNK pathway, affecting the serine phosphorylation of insulin receptor substrate 1 (IRS1) and thereby reducing the tyrosine phosphorylation of IRS-1. Leukotriene B4 (LTB4) may also reduce the tyrosine phosphorylation of IRS-1 through the JNK pathway [4]. Furthermore, excess lipids and metabolites are believed to be associated with insulin resistance. Increased release of FFAs from enlarged visceral fat cells leads to the accumulation of intracellular diacylglycerol (DAG). The accumulation of DAG may activate PKCε, inhibit the tyrosine phosphorylation of IRS1/2, and impair downstream signal transduction [40]. Moreover, excess FFAs may also have proinflammatory effects, activating the NF-kB pathway and increasing the production of inflammatory factors, including TNF-α, IL-1β, IL-6, MCP-1, and others [41, 42].

Insulin resistance may be a key factor linking abdominal visceral obesity to cardiovascular risk. It exacerbates chronic inflammation and affects lipid metabolism. Under normal circumstances, insulin promotes the degradation of apoB through a PI3 K-dependent pathway. However, insulin resistance may lead to reduced apoB degradation, and the interaction between excessive fatty acid transport and inadequate apoB degradation results in an elevated level of triglycerides in the blood [43, 44]. In addition, insulin resistance reduces the activity of LPL, leading to an increase in triglycerides and HDL in the blood. Prolonged insulin resistance may eventually lead to β-cell dysfunction during insulin secretion, causing hyperglycemia. Hyperglycemia may further stimulate the expression of inflammatory genes in macrophages and the characteristics of atherosclerosis through the glycolysis pathway and may also lead to the excessive accumulation of mitochondrial ROS. Mitochondrial dysfunction caused by insulin resistance may further exacerbate insulin signal transduction, affecting glucose entry into adipocytes and skeletal muscle cells [45, 46].

Ectopic fat deposition

In addition to VAT, ectopic fat includes perivascular adipose tissue (PVAT), epicardial adipose tissue (EAT), and renal perirenal fat, each with unique anatomical locations influencing the arteries in their vicinity. The distribution of ectopic fat tissue itself does not inherently negatively impact blood vessels; physiologically functioning ectopic fat also secretes adipocyte factors, preserving endothelial function, providing physical protection to vessels, and inhibiting the onset of atherosclerosis [47]. Adipose tissue also secretes vasoactive substances such as angiotensinogen (involved in blood pressure regulation), PAI-1 (which inhibits fibrinolysis and promotes thrombus formation), and leptin (elevating blood pressure through sympathetic nervous activation) [48]. However, abnormal deposition of ectopic fat tissue, including VAT and its associated deposits in the liver and epicardium, may contribute to increased atherosclerosis and cardiovascular disease [49].

The aorta, coronary artery, carotid artery and other blood vessels are surrounded by adipose tissue, known as perivascular adipose tissue (PVAT), which is related to cardiovascular disease (CVD) [50]. The number of brown adipocytes is very limited in adults. Interestingly, cold stimulation can convert WAT into beige adipose tissue (BeAT) through the browning process. The PVAT of the human aortic artery and coronary artery is also BeAT, so it is characterized by heat generation [51, 52]. Previous studies have reported that thermogenic aortic PVAT can improve impaired endothelial function in aging mice [53]. It was further confirmed that the lack of PVAT increased macrophage infiltration in the perivascular area of the aorta and increased the production of inflammatory cytokines, leading to increased vascular inflammation and atherosclerotic lesions in the aortic wall [54]. Many studies [55, 56] have shown that promoting the thermogenic effect of PVAT may inhibit the development of atherosclerosis. Endothelial dysfunction can reduce the expression of endothelial nitric oxide synthase (eNOS), reduce the production and bioavailability of NO, and thus have adverse consequences for vasodilation. The removal of PVAT reduced basal NO production in the small arteries of healthy individuals, indicating that PVAT contributes to the production of vascular NO [57]. Adiponectin normalizes endothelial function through a mechanism involving increased eNOS phosphorylation and controls blood pressure through an endothelium-dependent mechanism [58]. PVAT-derived adiponectin inhibits plaque formation by reducing the vascular inflammatory response [59].

However, under pathological conditions such as obesity, PVAT-derived inflammatory mediators may have adverse effects on the formation and stability of atherosclerotic plaques. Obesity increases the number and activation level of various resident immune cells in the PVAT, including macrophages, dendritic cells (DCs), T cells and B cells, which are locally regulated to contribute to the inflammatory state of the vascular wall [60–62]. At the same time, obesity promotes the expansion of adipose tissue, including PVAT, and increases the decomposition rate of basal fat, which also increases the release of FFAs and the secretion of proinflammatory factors into the circulation [63]. In addition, in obese rats induced by a high-fat diet, PVAT dysfunction can promote endothelial dysfunction by regulating the AMPK/mammalian rapamycin kinase target (mTOR) pathway [64].

The epicardial space is filled with embryonic adipose tissue similar to abdominal visceral fat, called epicardial adipose tissue (EAT). There is considerable confusion in the literature about these and other terms used to define intrapericardial and extrapericardial adipose tissue. Pericardial adipose tissue has been used to describe the sum of epicardial and pericardial adipose tissue. We believe that adipose tissue confined to the visceral layer of the pericardium should be called EAT [65]. The EAT has several important functions: it provides thermal insulation; as a buffer system, it absorbs the power that affects the heart; and it is a source of energy by providing free fatty acids to the heart. In an early study, Alexopoulos et al. [66] proved that EAT is associated with the presence of noncalcified plaques or plaques containing a mixture of calcium and areas supposedly a lipid-rich core. In a subsequent study, the correlation between EAT and plaque vulnerability was confirmed by noninvasive imaging [67, 68]. Recent ROMICAT studies have shown that EAT is independently associated with high-risk plaque characteristics in patients with suspected acute coronary syndrome [69].

Although VAT plays a major role in promoting atherosclerosis, EAT and PVAT may have local paracrine effects [70, 71]. The absence of fascia between the EAT and the adventitia of the coronary artery allows direct entry into the vascular wall of body fluids and cellular inflammatory mediators, which may promote the proliferation of vascular catheters and the growth of subendothelial atherosclerotic deposits [71]. More importantly, the presence of noncalcified plaques is associated with increased macrophage infiltration and neovascularization in EAT. Recently, integrated miRNA and genome-wide analyses of EAT in patients with coronary heart disease revealed upregulated expression of genes associated with antigen presentation, chemokine signaling and inflammation [72]. Similarly, in EAT, an imbalance between adiponectin secretion and proinflammatory factors was also observed [73, 74]. In addition, EAT also shows high turnover of FFAs (uptake and secretion), high lipolysis and increased concentrations of saturated fatty acids but lower concentrations of unsaturated fatty acids [75].

The combination of local and systemic mechanisms is likely to be the cause of atherosclerosis caused by VAT.

How laparoscopic sleeve gastrectomy (LSG) affects atherosclerosis

Overview of LSG

The accumulation of VAT is a crucial mechanism in the development of atherosclerosis. Consequently, weight reduction has emerged as a crucial strategy for mitigating the risk of atherosclerosis. Bariatric surgery has emerged as an effective method for reducing VAT mass and concurrently lowering the risk of atherosclerosis in people living with obesity. Bariatric surgery, also known as metabolic bariatric surgery (MBS), has undergone continuous refinement and development over the past few decades, establishing itself as a successful approach for treating obesity and its associated complications [76]. Bariatric

surgeries can be categorized into three types based on their surgical principles: pure restrictive procedures such as adjustable gastric banding (AGB), intragastric balloon (IGB), and vertical sleeve gastrectomy (VSG); malabsorptive procedures such as biliopancreatic diversion (BPD); and RYGB, BPD-DS, and OAGB/MGB [77–79]. With the development of minimally invasive laparoscopic techniques, VSG should be more accurately referred to as laparoscopic sleeve gastrectomy (LSG). In common bariatric surgery, LSG is known for its technical simplicity, feasibility and safety. For animal experiments, because it does not involve endoscopic techniques, it should still be called VSG.

Although LSG does not involve intestinal rearrangement, it still changes the anatomical structure of the gastrointestinal tract, resulting in weight loss and improved comorbidity through reduced energy intake and changes in gastrointestinal hormones and the intestinal flora. In a prospective study by Zhang and Zhu, people living with obesity who underwent LSG experienced a decrease in VAT from 1.33 kg to 1.03 kg 3 months postoperatively [80]. This conclusion was also confirmed in a study involving 49 people living with obesity, where VAT mass was reduced by nearly half 12 months after LSG [81]. In Elkan's study, patients who underwent laparoscopic sleeve gastrectomy (LSG) showed significant improvements in systolic and diastolic blood pressure, endothelial function, carotid intima–media thickness (CIMT), ankle–brachial index (ABI), and other early markers of atherosclerotic cardiovascular diseases 6 months postoperatively. This indicates that LSG can reduce the risk of atherosclerosis and decrease atherosclerosis-related risk factors [82].

In the following section, we will provide a detailed overview of the current mechanism by which LSG affects coronary atherosclerosis.

LSG alters energy balance to reduce VAT

Reduced stomach capacity leads to reduced food intake

After LSG, the remaining stomach has a volume of approximately 60–150 ml [83], leading to changes in postoperative eating habits and resulting in a significant reduction in energy intake. A decrease in stomach capacity enhances postprandial satiety, creating a state of negative energy balance and ultimately leading to the consumption of more adipose tissue. Although bariatric surgery was originally intended to limit food intake and cause malabsorption, there is evidence that bariatric surgery contributes the least to weight loss [84]. In contrast, one of the important methods of bariatric surgery is to change the energy balance and consume VAT actively by reducing hunger, increasing satiety during meals, changing food preferences and reducing intestinal absorption [85, 86].

In contrast, gastric emptying and intestinal transit seem to occur faster after VSG [87, 88]. The underlying mechanism is not clear but may include the production of very high intracavity gastric residual pressure, as well as hormone and nerve signal transduction. Mechanical factors are comprehensive factors that may not only affect satiety but also affect intestinal absorption and energy metabolism. (Insert Fig. 2).

Control of energy balance in the central nervous system (CNS)

An increase in satiety and a decrease in hunger after LSG are considered to be physiological and may be related to hypothalamic signals [89–91], vagus nerve signals [92, 93], and gastrointestinal hormones [94–97].

The arcuate nucleus of the hypothalamus contains two groups of neurons with opposite effects. The first group received pro-opiomelanocortin (POMC)-derived peptide stimulation through melanocortin receptor 4 (MC4R) on the periventricular nucleus, lateral hypothalamus and ventromedial nucleus to reduce food intake and increase energy consumption. The second group of neurons synthesizes neuropeptide Y (NPY), spine-associated protein (AgRP) and γ-aminobutyric acid, which increase food intake and reduce energy consumption via inhibition POMC [89]. In a mouse study [85], the mice were divided into three groups: Sham (ad lib) and Sham (pair-fed) with VSG and VSG. There was no difference in the number of NPY/AgRP-expressing neurons among the three groups. However, the number of POMC-expressing neurons in the VSG was significantly greater than that in the other two control groups. This finding may indicate that calorically restricted mice are hungry, while VSG mice are not hungry [90]. VSG may alter signal transduction from the gut to the hypothalamus and brainstem.

After VSG, the postprandial release of the postprandial anorexigenic hormone peptide YY (PYY) significantly increased but did not increase after AGB or caloric restriction. The L cells of the distal small intestine release PYY, which is thought to act on the arcuate nucleus of the hypothalamus to reduce food intake and through the vagus nerve to terminate the solitary nuclear tracking signal of satiety [94].

Nutrients that are partially digested from the stomach enter the small intestine, which subsequently leads to the release of various intestinal peptides by intestinal endocrine cells. These gastrointestinal peptides are critical for regulating metabolic homeostasis. The preproglucagon gene is expressed mainly in intestinal endocrine cells located in the ileum, distal colon, pancreatic α-cells, and discrete areas in the solitary tract nucleus. In the brain and intestine, posttranslational processing by

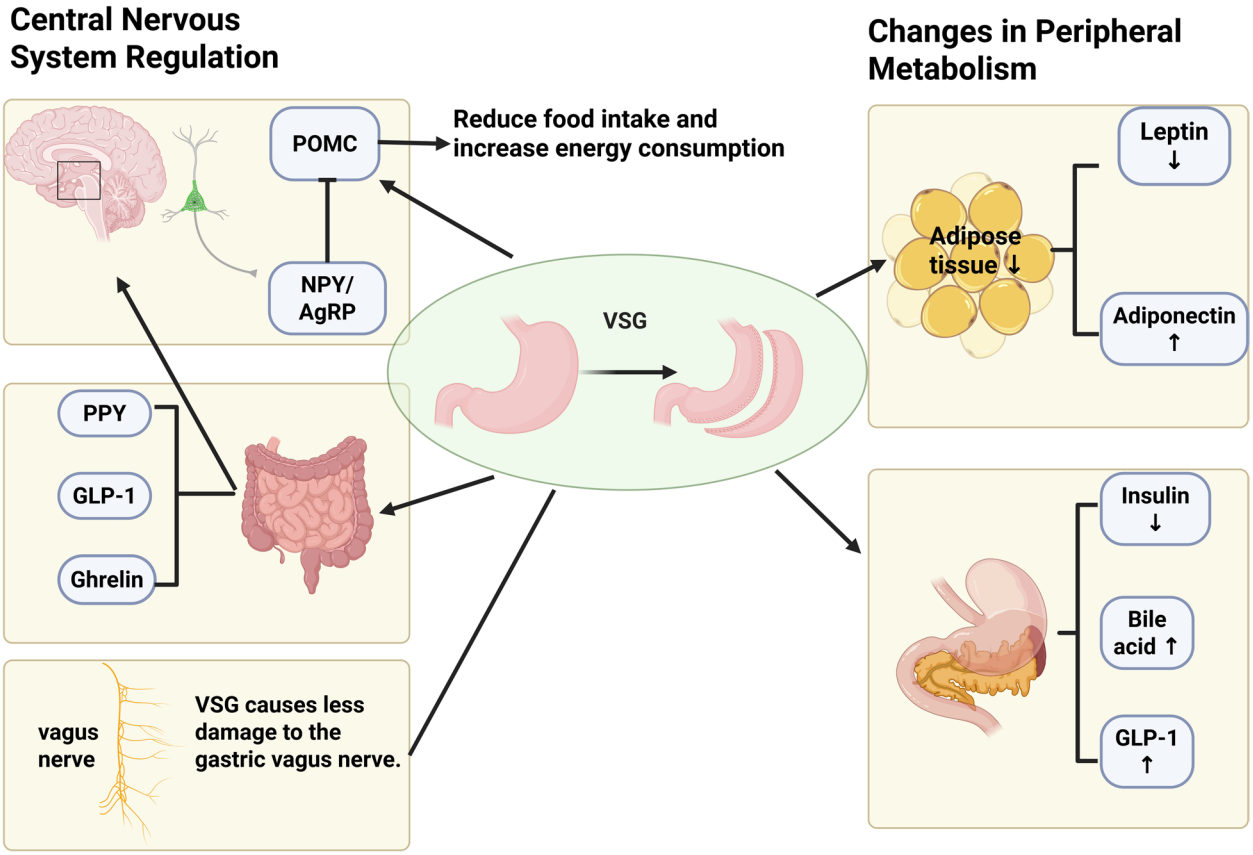

Fig. 2 LSG regulates energy metabolism through central and peripheral mechanisms. At the central level, LSG enhances hypothalamic POMC neuron activity while suppressing NPY/AgRP neuronal signaling to reduce appetite. The procedure has minimal impact on vagal nerve signaling pathways. Peripheral mechanisms involve significant alterations in gut hormone secretion: elevated GLP-1 and PYY levels suppress hunger, whereas reduced ghrelin secretion diminishes hunger signaling. Postoperative body composition remodeling is characterized by decreased visceral fat, accompanied by increased adiponectin and reduced leptin, which collectively improve insulin sensitivity and alleviate lipid metabolism disorders

prohormone convertase 1/3 leads to the production of glucagon-like peptide 1 (GLP-1), GLP-2, regulatory proteins and heparin-associated pancreatic polypeptide (PP) [95, 98, 99]. The physiology and role of GLP-1 in bariatric surgery are the most widely studied. GLP-1 has a wide range of physiological effects, including acting as a satiety factor and one of the two main incretin hormones that stimulate the secretion of insulin by pancreatic β-cells. In addition, GLP-1 has been found to reduce gastric emptying and inhibit glucagon secretion. After VSG, postprandial GLP-1 levels are significantly increased [91, 92]. It acts on GLP-1 receptors located in the hypothalamus, striatum, brainstem, substantia nigra, and other regions of the brain and reduces food intake by affecting the hypothalamus and brainstem [100]. At present, VSG can lead to an increase in GLP-1, and the underlying mechanism has been widely studied. In the absence of a shorter small bowel in the VSG, the increase in the levels of these gut hormones has been attributed to rapid gastric emptying [101].

Ghrelin is derived from a prohormone, preproghrelin, which consists of 117 amino acids [102]. Ghrelin, known for its appetite-stimulating effects, is secreted by neuroendocrine cells in the gastric oxyntic mucosa. It also plays a role in stimulating appetite in the hypothalamus and acylates growth hormone-releasing peptide (AG), serving as an endogenous ligand for the growth hormone secretagogue receptor (GHS-R1a) [103]. After VSG removes most of the ghrelin-secreting cells, patients with VSG exhibit decreased fasting and postprandial acyl and deacyl ghrelin levels at 6 weeks after surgery [104]. Similarly, a rodent model of VSG also showed a decrease in acyl ghrelin levels [105, 106]. The secretion of ghrelin is reduced after VSG resection of most gastric tissue, which is considered to be a mechanism for the beneficial effect of VSG. However, mice genetically deficient in ghrelin exhibit normal body weight loss and improvements in glucose tolerance in response to VSG, suggesting that this decrease in ghrelin, in and of itself, is not necessary for rodents

to lose weight or improve glucose tolerance after VSG [105].

The sensory information of the stomach is transmitted to the brainstem through the gastric vagal afferent via the "solitary-reticular ingestion system", for the control of ingestive behavior has been previously established [107, 108]. In this signaling system, the vagal afferent cell body is located in the nodular ganglion, and approximately 70% of vagal afferents innervate the abdominal viscera, most notably the stomach and intestines [93]. In the VSG, vertical gastrectomy causes distal gastric vagus nerve injury [109]. Therefore, the gastrointestinal tract selectively affects food intake through the vagus nerve, which is likely to change after weight loss surgery. One study [92] showed that both the VSG and RYGB procedures impaired vagus nerve innervation of the stomach. However, the nature of this damage and the subsequent consequences for the posterior brain signal circuit are different between each process. The results of this study showed that RYGB, rather than the VSG, triggered the activation of microglia in the vagus nerve structure and reshaped gut–brain communication. Consistently, previously published studies and the results of this study showed that the VSG caused less damage to the gastric vagus nerve [110, 111].

Intestinal hormones and other peripheral participants

VSG can cause a series of changes in hormone secretion, especially in the secretory function of the intestine and other digestive organs, and is related to the mechanism of successful surgical metabolism. In this section, we will discuss the changes and potential roles of various peptides secreted from the small intestine, pancreas, and bile in the metabolic success of bariatric surgery.

Insulin is a key regulator of glucose homeostasis, and its function is to stimulate peripheral blood glucose storage by increasing glucose uptake and stimulating glycogen synthesis. In addition, the increase in glucagon balance by insulin inhibits postprandial hepatic glucose production. It has been widely reported that fasting serum insulin levels are reduced in VSG patients [96, 112, 113]. It is closely related to the degree of postoperative weight loss. At the same time, the C-peptide level also decreased after VSG [112]. Therefore, changes in insulin levels reflect a decrease in secretion under fasting conditions rather than an increase in clearance.

Bile acids can also act as hormones to activate two different receptors: a cell surface membrane-bound G protein-coupled receptor (TGR5) [114, 115] and a nuclear transcription factor, farnesoid X receptor (FXR) [116, 117]. Studies have shown that the activation of TGR5 can stimulate the secretion of GLP-1 by intestinal L-cells [118] and by acting on receptors in muscle and brown adipose tissue. It has been reported that bile acid levels increase after bariatric surgery. However, it is important to note that bile acids come in many different forms, and only cholic acid (CA)-derived bile acids (DCA, TCA, and GCA) reportedly increase during fasting after VSG [119]. One study demonstrated that TGR5 signaling is required to maintain the beneficial effects of VSG on weight loss, glucose tolerance, hepatic steatosis, energy expenditure, and GLP-1 secretion [120].

Improving body composition and lipid homeostasis lowers cardiovascular risk

Following LSG, weight loss is accompanied by changes in body composition. The reduction in adipose tissue coincides with an increase in lean body mass [121]. A retrospective observational study combined with Mendelian randomization analysis systematically explored the mechanisms by which distinct body compositions influence lipid metabolism and atherosclerosis through specific inflammatory pathways [122]. The study revealed that adipose tissue and lean tissue exert bidirectional regulatory effects on cardiovascular metabolism via differentiated inflammatory mediator networks: increased adipose tissue elevates triglyceride levels by raising leptin and reducing adiponectin, whereas lean tissue improves the lipid profile by lowering leptin and insulin while enhancing adiponectin [122].

In individuals with identical genetic backgrounds, obesity-related metabolic risks depend not only on the degree of adipocyte hypertrophy but also critically on their capacity for hyperplastic compensation [123]. The study [123] found that when fat cells grow larger from excess energy, if their number decreases (called "hypoplastic obesity"), it causes problems like mitochondrial failure and higher oxidative stress. This leads to fat buildup in the liver and body-wide insulin resistance. On the other hand, people whose fat cells can multiply (hyperplastic obesity) keep their metabolism stable by storing more fat in their fat cells. Notably, similar mechanisms may operate during body composition remodeling following weight-loss interventions. The reduction in VAT after LSG not only directly alleviates lipid overload but also likely reverses pro-inflammatory pathways associated with hypoplastic obesity by modulating adipokine networks.

A decrease in body weight after LSG was accompanied by a decrease in VAT and ectopic fat (including PVAT), as well as improvements in other metabolic parameters. These conditions include abnormal lipid metabolism, insulin resistance, inflammation, endothelial dysfunction, adipocytokine imbalance and inflammasome obesity and can even occur independently of weight loss [124]. Weight loss and VAT loss are important mechanisms for

the improvement of a series of cardiovascular diseases by LSG, which is the core topic of this paper.

The LSG alters the intestinal microbiota

Most of the bacterial species in human and mouse intestines belong to Bacteroidetes and Firmicutes, as well as a small number of bacterial phyla, such as Actinobacteria, Proteobacteria and Verrucomicrobia, as well as methanogenic archaea, mainly M. stutzeri [125]. The intestinal microbiota has a variety of functional characteristics and affects host physiology inside and outside the intestine. In the state of obesity and CAD, the incidence of intestinal microbiota has changed to varying degrees. Researches have shown that people living with obesity seem to have fewer Bacteroidetes than normal-weight individuals [126, 127].

Different microbial composition changes have been described under CAD conditions. The characteristic changes were a significant increase in Lactobacillus (belonging to the phylum Firmicutes) and a significant decrease in Bacteroidetes[128]. However, randomized controlled trials using antibiotics against these microbial pathogens have not shown any clinical benefit in reducing morbidity or mortality in patients with CHD [129]; therefore, the pathogenic mechanisms of these microorganisms remain unclear.

After bariatric surgery, there are significant alterations in the composition of the gut microbiota, characterized by increased microbial diversity, changes in the relative abundance of specific bacterial genera, and improvements in the spatial organization and stability of the gut microbiota. Following LSG, there is an increase in the α-diversity of the gut microbiota, with an increase in the ratio of Firmicutes to Bacteroidetes and a significant increase in Akkermansia muciniphila, a bacterium known for its role in inhibiting adipose tissue accumulation and metabolic abnormalities [130, 131].

Overall, alterations in the gut microbiota after bariatric surgery impact energy absorption. The decrease in the ratio of Firmicutes to Bacteroidetes may contribute to the reduction in VAT, possibly as a result of the interaction between bacterial metabolic byproducts and the brain. However, there is no consensus on postoperative changes in the gut microbiota, and the mechanisms influencing the reduction in VAT have yet to be confirmed [131].

Conclusion

Bariatric surgeries, predominantly LSG, have emerged as the principal intervention for managing complications in people living with obesity. Although mitigating the risk of atherosclerosis is not typically the primary objective of these procedures, their undeniable efficacy in this regard is noteworthy. Patients undergoing LSG experience a substantial reduction in energy intake attributable to diminished gastric capacity. Concurrently, the reconstructed gastrointestinal tract induces alterations in the secretion of intestinal hormones, fostering decreased appetite, diminished fat accrual, and heightened satiety. Simultaneously, shifts in the gut microbiota influence the distribution of abdominal adipose tissue. After LSG, a recovery of the energy balance ensues, resulting in a reduction in the VAT. This reduction is concomitant with diminished blood lipid levels, alleviation of chronic inflammation, and enhanced insulin sensitivity. The amelioration of these complications collectively serves to attenuate the risk of atherosclerosis. From the standpoint of sustained weight management postsurgery, the risk of atherosclerosis is conspicuously attenuated. The impact of LSG on atherosclerosis extends beyond VAT to include the influence of other adipose tissues, including pericardial and vascular adipose tissues, on major arteries. Nevertheless, VAT, as the primary benefit of LSG, has the most pronounced influence on atherosclerosis. Atherosclerosis encompasses numerous risk factors, including hypertension, diabetes, and hyperlipidemia, all of which are complications of obesity. Consequently, the benefits of LSG include a mere reduction in the risk of atherosclerosis.

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Juan Xu and Heyue Wang drafted and revised the manuscript. Xiaomin Zhang and Bin Han collected relevant papers and helped to revise the manuscript. Xiaomin Zhang designed the charts. All authors contributed to the article and approved the submitted version.

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Availability of data and materials

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

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Competing interests

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