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# Obesity and the obesity paradox in abdominal aortic aneurysm

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Obesity, characterized by its complexity and heterogeneity, has emerged as a significant public health concern. Its association with increased incidence and mortality of cardiovascular diseases stems not only from its complications and comorbidities but also from the endocrine effects of adipose tissue. Abdominal aortic aneurysm (AAA), a chronic inflammatory condition, has been closely linked to obesity. Intriguingly, mild obesity appears to confer a protective effect against AAA mortality, whereas severe obesity and being underweight do not, giving rise to the concept of the “obesity paradox”. This review aims to provide an overview of obesity and its paradoxical relationship with AAA, elucidate its underlying mechanisms, and discuss the importance of preoperative weight loss in severely obese patients with AAA.

## KEYWORDS

abdominal aortic aneurysm, obesity, obesity paradox, prehabilitation, aging

## 1 Introduction

Obesity, characterized by abnormal or excessive fat accumulation, constitutes not only a metabolic disorder but also a chronic inflammatory, degenerative, and psychosocial ailment that poses a significant threat to public health (1–4). Particularly, central obesity has been strongly associated with the development of cardiovascular diseases and increased mortality (5–7).

Abdominal aortic aneurysm (AAA), likened to an untimed bomb within the body, is defined as a 50% dilation of the abdominal aorta, typically exceeding 3 cm. It is recognized as a chronic inflammatory degenerative disorder of the aorta (8). Risk factors for AAA encompass aging, hypertension, hyperlipidemia, smoking, and a family history of AAA (9). While obesity traditionally isn't regarded as a risk factor for AAA, there's a growing body of literature suggesting a correlation between weight gain and a heightened incidence of AAA and associated mortality. However, studies regarding the impact of obesity on AAA present conflicting findings (10).

Obesity encompasses not only the accumulation of fat cells in the body but, more significantly, is often accompanied by adverse lifestyle choices and various comorbidities. These factors collectively influence the initiation, progression, and prognosis of AAA. Consequently, analyzing obesity as a singular variable leads to complexity and inaccuracies in clinical observations and outcomes.

In this review, our aim is to explore the intricate relationship between obesity and AAA, elucidating the underlying mechanisms. Additionally, given the elevated risk of adverse events during the perioperative period, perioperative weight loss in obese patients has garnered considerable attention. Therefore, we intend to summarize the current published research on the timing and methods of weight loss, aiming to delineate the potential role of intentional weight loss in the prevention and management of AAA, and to inspire future research (Table 1).

## 2 Obesity to AAA: foe or friend?

Although obesity is not explicitly designated as a risk factor for AAA in current guidelines, several clinical studies have suggested that excessive fat accumulation does indeed heighten the risk of developing AAA. For instance, a case-control study involving 504 participants revealed a positive correlation between BMI and increasing aortic diameter at the superior mesenteric artery (SMA) segment (10) (Table 1). Additionally, various methods of evaluating obesity have shown a corresponding increase in AAA incidence with the severity of obesity.

When stratifying obese patients based on the degree of obesity, an intriguing trend emerges concerning the perioperative mortality of AAA. A retrospective study involving 5,455 AAA patients revealed that morbidly obese individuals ( $BMI > 34 \text{ kg/m}^2$ ) exhibited higher 30-day mortality rates in both open aneurysm repair (OAR) and endovascular aneurysm repair (EVAR) procedures compared to non-obese patients, including those with milder obesity (24). Additionally, for every  $1 \text{ kg/m}^2$  increase in BMI, the risk of 30-day death in hospitalized patients undergoing repair for ruptured abdominal aortic aneurysm was significantly elevated by 1.08 (95% CI, 1.01–1.17;  $P=0.04$ ) (23).

However, patients classified as mildly obese displayed the lowest mortality rates post-AAA surgery, even lower than those with normal weight (25, 26). Further investigation through a retrospective analysis of 9,479 patients undergoing OAR revealed that individuals categorized as overweight ( $BMI: 25\text{--}30 \text{ kg/m}^2$ ) or mildly obese ( $BMI > 30 \text{ kg/m}^2$ ) did not exhibit additional surgical mortality associated with BMI until BMI surpassed  $34 \text{ kg/m}^2$  (27). Interestingly, mortality in AAA patients does not correspondingly increase with the severity of obesity; it is lowest in those with mild obesity but elevated in patients with low weight or excessive obesity. Although certain studies have concluded that obesity does not exert a statistically significant effect on the perioperative mortality of AAA, this may stem from a lack of BMI stratification among patients. Nevertheless, these studies have consistently indicated that both low body weight and severe obesity predispose individuals to increased perioperative complications such as renal insufficiency and wound infections, thereby contributing to poorer

prognoses in AAA patients (18–21). This phenomenon, akin to the “obesity paradox” observed in other cardiovascular diseases, underscores the complex interplay between obesity and AAA outcomes (28–30).

Given the inconsistent role of obesity in the epidemiology and prognosis of AAA, we will address on the following aspects

## 3 Potential mechanism of obesity aggravating AAA

As outlined in Section 2 and corroborated by Table 1, it is evident that obesity augments the incidence of AAA. Numerous clinical studies have substantiated a positive correlation between the degree of obesity and the diameter of the abdominal aorta in AAA patients, irrespective of the method used to evaluate obesity (10, 13, 16, 17).

Obesity, recognized as a chronic degenerative disease, manifests cardiovascular implications at an earlier age compared to individuals with normal weight, essentially reflecting accelerated systemic aging (31). Senescent cells accumulate with aging, obesity, and diabetes, particularly within adipose tissue depots, encompassing subcutaneous, visceral, and intramuscular spaces (8, 32). Excessive energy intake disrupts the delicate energy balance, leading to hypertrophy and hyperplasia of adipose tissue around various organs, including the liver, heart, muscle, kidney, pancreas, and inducing insulin resistance (33). Moreover, obesity, hypercholesterolemia, hypertension, and high-fat diets contribute to an inflammatory milieu, oxidative/nitric stress, mitochondrial dysfunction, endothelial apoptosis, macromolecular damage, and vascular wall senescence, consequently heightening cardiovascular risk and disease, including AAA (34).

Similarly, AAA, characterized as a chronic inflammatory degenerative ailment, essentially represents vascular senescence, with its prevalence escalating with age (35, 36). Experimental studies have delineated transcriptional alterations in abdominal aortic tissue during aging-induced AAA, characterized by smooth muscle cell loss, leukocyte adhesion, inflammation, and accumulation of senescent cells in the vascular wall and perivascular adipose tissue (PVAT) (37). Pathological changes observed in human AAA closely resemble those occurring in the abdominal aorta due to obesity (38). Furthermore, experiments have underscored the impact of preaging adipocyte secretions on vascular wall cell phenotype and function, mirroring observations in aneurysmal vessel walls (39).

### 3.1 Adipose tissue in the pathological state results in high AAA morbidity and mortality

As obesity progresses, human adipocytes not only undergo hypertrophy and hyperplasia but also transition from a physiological to a pathological state, thereby contributing to endocrine disorders associated with severe obesity (40). The adipose tissue in the human body comprises two main categories, primarily subcutaneous adipose tissue (SAT) and visceral adipose

TABLE 1 The relationship between obesity and abdominal aortic aneurysm.

The relationship between obesity and abdominal aortic aneurysm morbidity							
Obesity Index	Definition	Obesity Measure	Subjects	Abdominal Aortic Segments	Aortic Diameter Measurement Method	Relationship with AAA	Ref
Body Mass Index (BMI)	Weight (kg)/Height <sup>2</sup> (m <sup>2</sup> )	Overall level of obesity	Human (504 participants)	Superior mesenteric artery (SMA) segment; Aortic midpoint segment; Aortic bifurcation segment	Computerized Tomography (CT)	BMI is positively associated with increasing aortic diameter at the SMA segment (standardized $\beta=0.68$ $p<0.01$ )	(10)
			Human (3,056,455 participants)	The greater of orthogonal and transverse ultrasound measurements of the infrarenal abdominal aorta	Ultrasound	BMI>25 is significantly associated with AAA prevalence (OR=1.20[95% CI, 1.17-1.22], $P<0.001$ )	(11)
Fat-free Mass Index	Assessed using bioelectrical impedance Technique, fat-free mass (kg)/Height <sup>2</sup> (m <sup>2</sup> )	The percentage of the body mass corresponding to fat-free mass	Human (367703 participants)	Not available	Not available	There was significant evidence that fat-free mass index was inversely associated with abdominal aortic aneurysm [OR=0.64 (95% CI, 0.42-0.95), $P=0.03$ ].	(12)
Waist circumference (WC); Waist-to-hip ratio (WHR)	WC is measured at the level between the lowest rib and iliac bone; WHR is the WC divided by the hip circumference	Central (abdominal) obesity	Human (12203 participants)	The maximum diameter of the infrarenal aorta	Ultrasound	Waist circumference [OR=1.14 (95% CI, 1.06-1.22), $P<0.001$ ] and waist-to-hip ratio [OR=1.22 (95% CI, 1.09-1.37), $P<0.001$ ] were independently associated with AAA and aortic diameter, especially for AAA $\geq 40$ mm [OR=1.53 for waist-to-hip ratio (95% CI, 1.26-1.85), $P<0.001$ ].	(13)
Fat Percentage (BF%)	Measured by hydrostatic weighing, predicted by body skinfolds measurements or by DXA whole body scans	The percentage of the body mass corresponding to fat mass	Human (504 participants)	Superior mesenteric artery segment; Aortic midpoint segment; Aortic bifurcation segment	Computerized Tomography (CT)	Positively associated with increasing aortic diameter at the SMA segment (standardized $\beta=0.12$ $p<0.01$ )	(10)
Periaortic Adipose Tissue Volume	The volume of adipose tissue at mid-abdominal aorta	ectopic fat depots and central obesity	Human (3000 participants)	A level 5 cm above the aortoiliac bifurcation	CT	Periaortic fat volume was associated with aortic dimensions in abdomen ( $P<0.001$ )	(14)

(Continued)

TABLE 1 Continued

The relationship between obesity and abdominal aortic aneurysm morbidity							
PVAT Density	The ratio between the number of fat pixels inside ROI and the area of the ring	Ectopic fat depots	Human (341 participants)	The maximum length between opposite walls on AAA main axis	CT	Individual PVAT differences were positively correlated with aortic volume. (P=0.006) The presence of aneurysms was an independent predictor of increased differences in PVAT <i>in vivo</i>	(15)
Epicardial Adipose Tissue volume (EATV)	The volume of visceral adipose tissue that is located between the pericardium and myocardium	Ectopic fat depots	Human (237 patients with infrarenal and fusiform AAA)	The difference between the initial and last maximal short-axis diameter of AAA	CT	AAA expansion rate is positively correlated with EATV index (R =.237, P <.001). Initial aneurysm diameter and EATV index > 60.3 cm <sup>3</sup> /m <sup>2</sup> were significantly correlated with AAA dilation rate (P<0.001)	(16)
Intramuscular Fat	Using threshold method with semiautomatic segmentation procedure	Ectopic fat depots; Associated with postoperative recovery	Human (94 AAA patients undergone EVAR)	Difference in aneurysm volume before and after EVAR; Maximum aneurysm diameter	CT	Patients with more intramuscular fat had a high risk of aneurysm dilation.	(17)
The relationship between obesity and abdominal aortic aneurysm mortality							
Body Mass Index (BMI)	Weight (kg)/Height <sup>2</sup> (m <sup>2</sup> )	Overall level of obesity	Human (33082 AAA patients)	Not available	Not available	There is no significant difference in mortality between the obesity and non-obesity groups undergoing OAR and EVAR [OAR, 2.9% vs 3.2% (P = .50); EVAR, 0.5% vs 0.6% (P = .76)]. However, risk of renal failure and wound infections is higher in obese group.	(18)
			Human (33082 patients with pararenal and thoracoabdominal aortic aneurysms)	Not available	Not available	There exist no significant differences between the obese and nonobese patients undergoing FB-EVAR in 3-years survival (83% ± 5% vs 75% ± 4%; P = 0.16), although 2 and 12 months QOL scores	(19)

(Continued)

TABLE 1 Continued

The relationship between obesity and abdominal aortic aneurysm morbidity							
The relationship between obesity and abdominal aortic aneurysm mortality							
						showed higher in the obese patients.	
			Human (80 AAA patients undergoing elective EVAR)	Not available	Not available	Obesity(BMI $\geq$ 30) have little influence on outcomes after EVAR during 2 years of follow-up ( $p = 0.688$ ).	(20)
			Human (2201 AAA patients)	Not available	Not available	Obesity(BMI $\geq$ 30) independently predicts increased cardiac (OR=4.5 for obesity III, $P=0.045$ ) and renal complications (OR=6.3 for obesity III, $P<0.001$ ) after open AAA repair and predicts increased wound complications after both open repair(OR=2.4 for obesity I, $P=0.002$ ) and EVAR(OR=3.1 for obesity I, $P=0.026$ ), despite no statistically difference in 30 day mortality.	(21)
			Human (103,972 AAA patients)	Not available	Not available	BMI is positively associated with AAA mortality among men patients [HR=3.81(95% CI, 1.39–10.49), $P=0.01$ ]	(22)
			Human (202 patients with ruptured AAA)	Not available	Not available	For every 1 kg/m <sup>2</sup> increase in BMI, the risk of 30-day death in hospitalized patients with rAAA repair was significantly increased by 1.08 (95% CI, 1.01-1.17; $P = 0.04$ ).	(23)
			Human (5455 AAA patients)	Not available	Not available	The 30-day mortality rates of OAR (7.3%) and EVAR (2.4%) were higher in morbidly obese patients than in obese patients	(24)

(Continued)

TABLE 1 Continued

The relationship between obesity and abdominal aortic aneurysm morbidity	
The relationship between obesity and abdominal aortic aneurysm mortality	
	(3.9%, 1.5%) or non-obese (3.7%, 1.1%).
	(25)
	Trends in BMI were negatively and significantly associated with AAA mortality in both male and female (P=0.0039).
	(26)
	Class I obese (BMI 25.1-30) patients have a significantly lower 30-day risk of death compared to normal weight patients (P<0.05).
Not available	Not available
Not available	Not available
Human	Human (7543 AAA patients)

tissue (VAT). Predominantly composed of white adipocytes and often indicated by waist circumference, VAT is strongly linked to dyslipidemia and hypertension. Clinical studies have consistently demonstrated a significant association between increased VAT and a heightened risk of incident AAA (40–42).

Additionally, there exists a correlation between visceral abdominal adiposity and the volume and density of abdominal periaortic adipose tissue, which is directly related to the size of the aorta (14, 15, 43). This relationship may stem from the direct action of adipose tissue in its pathological state on the abdominal aorta, which can be concluded as an aging process. Key mechanisms include:

Firstly, obesity enhances the production of reactive oxygen species (ROS), resulting in oxidative stress. This oxidative damage accelerates endothelial dysfunction and promotes vascular stiffness, both of which are hallmarks of vascular aging and can eventually lead to AAA (44).

Moreover, adipose tissue in obese individuals secretes pro-inflammatory cytokines such as TNF- $\alpha$ , IL-6, and MCP-1. These cytokines induce a chronic inflammatory state that contributes to vascular aging by promoting endothelial cell apoptosis and reducing the regenerative capacity of vascular cells, processes that have been shown to cause AAA (45, 46).

Furthermore, alterations in adipokines derived from adipose tissue that contribute to aortic remodeling in both AAA patients and experimental models of AAAs can be considered manifestations of vascular aging (37). Some adipokines, such as leptin, and adiponectin, have been strongly associated with AAA diameter (13, 47). Leptin, a highly secreted adipocytokine by PVAT, is considered a proinflammatory factor that elevates levels of cytokines such as TNF- $\alpha$ , IL-6, and IL-12 (48–50). Research suggests that leptin from PVAT promotes AAA formation through IL-18-mediated smooth muscle cell loss, apoptosis, and induced vascular remodeling (51, 52). Pathological PVAT may also exacerbate endothelial dysfunction in diet-induced obese mice due to increased NADPH oxidase-derived oxidative stress and the production of proinflammatory cytokines (53). Additionally, resistin, omentin and vaspin have been shown to be deposited and induce endothelial cell dysfunction through paracrine signaling and other mechanisms (54). Another adipokine derived from PVAT, chemerin, has been shown to exacerbate experimental AAA by inducing endothelial dysfunction via targeting NAD(P)H oxidase in high-fat diet mice (55–57) (Figure 1).

### 3.2 Comorbidities and complications along with severe obesity results in high AAA morbidity and mortality

A previous study indicated that the risk of cardiovascular disease associated with a high BMI or increased waist circumference is primarily mediated by altered intermediate risk factors, such as atherosclerotic dyslipidemia and hypertension (12, 64). These factors may collectively contribute to the elevated morbidity of AAA. Lipid accumulation products have emerged as a stronger prognostic marker for all-cause cardiovascular morbidity

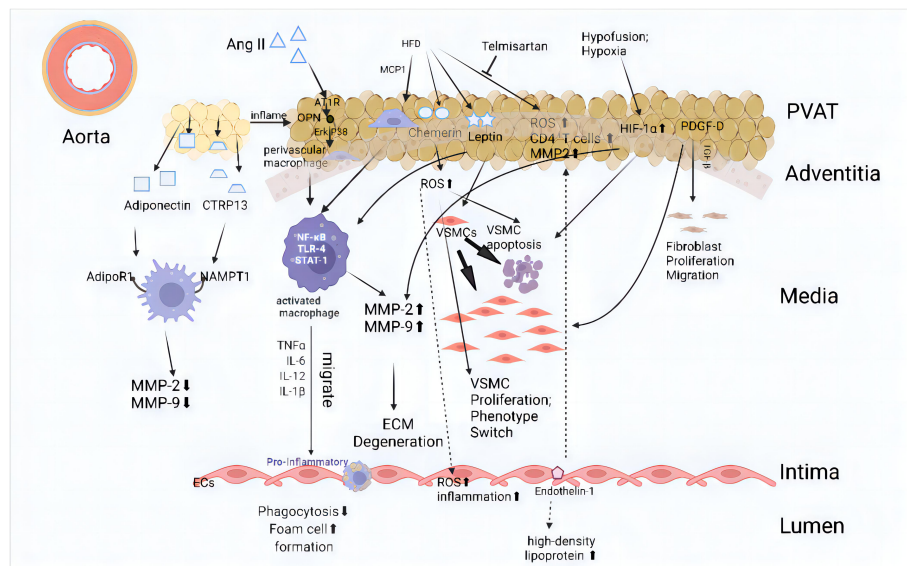


FIGURE 1

Mechanism of adipose tissue action on all layers of the abdominal aorta Internal or external environmental changes such as hypoxia and a high-fat diet can impact adipose tissue, leading to pathological changes and the release of adipokines. In a physiological state, perivascular adipose tissue (PVAT) can cause a full-thickness lesion of the arterial wall from the outside to the inside. The main manifestations include the aggregation of inflammatory cells, increased reactive oxygen species (ROS), changes in vascular smooth muscle cell (VSMC) phenotype, endothelial cell dysfunction, and extracellular matrix (ECM) degradation. These changes ultimately exacerbate abdominal aortic aneurysm (AAA). The main pathways include (1): Angiotensin II (Ang II): Ang II interacts with AT1R, triggering the OPN and Erk1/2 $\beta$  pathways, which leads to macrophage activation. This activation promotes the release of pro-inflammatory cytokines such as TNF $\alpha$ , TLR-4, and STAT-1, eventually resulting in ECM degeneration and increased endothelial cell inflammation (58–60) (2). High-Fat Diet (HFD): HFD induces the secretion of chemerin, leptin, and MCP1, which promote VSMC proliferation, apoptosis, and phenotype switching (57, 59, 61). Additionally, this process increases ROS and inflammatory responses within the vascular wall (3). Hypoxia and Hypofusion: Conditions like hypoxia induce HIF-1 $\alpha$  expression, promoting VSMC apoptosis and the release of MMP-2 and MMP-9. These changes further contribute to ECM degeneration and fibroblast proliferation and migration (62, 63). AT1R, Angiotensin II type 1a receptor; CTRP13, C1q/tumor necrosis factor (TNF)-related protein-13; ECM, Extracellular Matrix; HFD, High-fat diet; MCP-1, Monocyte chemoattractant protein-1; MMP, Matrix metalloproteinase; NAMPT1, Nicotinamide Phosphoribosyl-Transferase 1; OPN, Osteopontin; PDGF-D, Platelet-derived Growth Factor D; TGF- $\beta$ , Transforming Growth Factor- $\beta$ ; VSMC, vascular smooth muscle cell. (This figure is supported by Biorender).

and mortality compared to BMI, and have been associated with atherosclerosis, as evidenced in a retrospective study involving 9,180 participants (65). Additionally, both a prospective study and a multicenter retrospective analysis have independently confirmed a significant association between increased levels of lipoprotein(a) and the occurrence of AAA (66, 67). Furthermore, most AAAs are considered to represent end stages of atherosclerosis which is positively associated with lipoprotein level (68). Compensatory dilated remodeling, an essential component of atherosclerosis, is intended to delay the development of overt luminal compromise (69).

Additionally, findings from the Framingham Heart Study indicate that 60 to 70% of cases of essential hypertension can be attributed to obesity (70). Moreover, researchers suggest that obesity, characterized by elevated levels of leptin and decreased levels of adiponectin, may disrupt blood pressure regulation (71, 72). This imbalance in blood pressure regulation, in turn, weakens the arterial wall and increases arterial pressure, ultimately leading to arterial deformation and changes in hemodynamics, which can contribute to the progression of AAA (73–75).

Furthermore, individuals with abdominal obesity often lead unhealthy lifestyles, characterized by higher rates of smoking and

lower levels of physical activity. These lifestyle factors also play a significant role in the onset and progression of AAA (76, 77).

## 4 The obesity paradox in AAA — is obesity a true friend?

When regression analyses were conducted to identify risk factors related to global AAA mortality, BMI exhibited a negative linear association with AAA mortality ( $P \leq 0.007$ ), despite some studies presenting differing conclusions (18, 20, 25). However, upon stratification based on the degree of obesity, the protective effect of overweight or mild obesity on the prognosis of AAA was revealed, contrary to its epidemiological effect on AAA incidence. For instance, a case-control study involving 7,543 patients with AAA found that class I obese individuals (BMI 25.1–30 kg/m<sup>2</sup>) had a significantly lower 30-day risk of death compared to normal weight patients ( $P < 0.05$ ) (26).

Furthermore, a meta-analysis of 92,525 patients undergoing vascular surgery corroborated these findings, showing that patients with a BMI of 25–29.9 kg/m<sup>2</sup> exhibited the lowest overall mortality and had fewer cardiac and respiratory complications 30 days after

surgery (30). Importantly, this phenomenon extends beyond OAR to EVAR. A meta-study of 14,971 patients undergoing AAA surgery (including 11,743 EVAR cases) confirmed that obese patients had lower 30-day mortality (1.5%) compared to nonobese patients (2.2%) undergoing EVAR (78). This phenomenon is referred to as the obesity paradox, and possible mechanisms include:

As a chronic inflammatory disease, AAA exhibits high metabolic dynamics (79). Weight gain and overall obesity are often indicative of a positive long-term energy balance, where energy intake surpasses energy expenditure, thereby counteracting the energy expenditure associated with chronic inflammation and delayed vascular aging (80). Research from heart failure has shed light on the obesity paradox, which can be attributed to impaired fatty acid oxidation, characterized by mitochondrial dysfunction, reduced availability of essential cofactors such as coenzyme A or carnitine, downregulation of  $\beta$ -oxidase, and increased dependence on alternative substrates such as glucose and ketone bodies (81). The concept of supporting myocardial energetics by increasing fat intake has emerged as an important adjunctive treatment for heart failure.

Galectin 1, a member of the lectin family highly expressed in adipose tissue, has been found to exacerbate obesity in high-fat diet mice by increasing PPAR $\gamma$  expression and activation (82). However, it has also been found to be protective against AAA and atherosclerosis (83). This protective effect is attributed to the attenuation of foam cell formation and mitochondrial dysfunction in vascular smooth muscle cells (VSMCs), as well as the increase in systolic VSMCs in aortic tissue. The secretory function of adipose tissue can further reduce extracellular matrix fibrosis and macrophage infiltration/activation, while enhancing angiogenic potential, thus potentially playing a protective role in the cardiovascular system. However, the specific mechanisms underlying these effects require further exploration (84).

However, obesity, being a multifaceted disease, not only presents numerous comorbidities but also exerts a multifaceted impact on AAA mortality. The current study primarily utilized BMI as an indicator of obesity evaluation to explore its relationship with AAA, without considering the impact of other medical and medication histories. Therefore, whether obesity can be considered a true friend remains a complex and nuanced question that warrants further investigation.

#### 4.1 Obesity paradox caused by previous history – medical and medication history

The potential mechanism underlying the obesity paradox may indeed be rooted in timely lifestyle management and medication for obesity-related complications. Often regarded as a silent killer, obese patients with AAA are initially diagnosed and treated for obesity-related comorbidities and complications.

Prospective trials have demonstrated a positive correlation between the incidence of AAAs and BMI as well as waist circumference, similarly observed with diabetes (85, 86). However, a threshold for AAA incidence is noted as waist circumference increases, attributed to the protective effect of diabetes on AAA (42, 87, 88). Despite diabetes being a recognized

risk factor for cardiovascular disease, it exhibits an inverse association with the onset, development, and mortality of AAA (87–90). Notably, the protective effect of diabetes is heightened when obesity is controlled (87). One explanation for this phenomenon lies in the usage of hypoglycemic agents, such as metformin and Dapagliflozin (an SGLT-2 inhibitor), which exert anti-inflammatory and anti-aging effects, influencing mechanisms involved in the formation of both experimental and clinical AAA (91–93).

Furthermore, while dyslipidemia and atherosclerosis promote the occurrence and incidence of AAA, vascular calcification has been shown to stabilize the aortic aneurysm wall, potentially preventing AAA dilatation and reducing the risk of rupture and mortality (94, 95). It is demonstrated that established atherosclerosis accelerates AAA growth is limited (96). This discrepancy may stem from different phenotypes between substantial atherosclerosis and clinically insignificant atherosclerosis in AAA patients (8). Moreover, the use of lipid-lowering drugs, such as statins, may contribute to this phenomenon. Nevertheless, calcification has been associated with medial layer degradation and reduced AAA wall tissue content. The mismatch in material compliance between calcification and wall tissue leads to local high stress concentration in adjacent tissue areas, ultimately increasing the risk of AAA rupture (97, 98). The specific mechanism still needs to be further explored.

Furthermore, angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs), two common antihypertensive agents, have been found to be inversely associated with AAA mortality (58). Telmisartan, an angiotensin-converting enzyme inhibitor known for its antihypertensive properties, has been demonstrated to prevent the development of experimental AAA by inhibiting the angiotensin II type 1a (AT1a) receptor. However, the clinical treatment effect of telmisartan for small AAA is not significant (99, 100).

#### 4.2 Obesity paradox caused by obesity evaluation index—BMI paradox

BMI has traditionally served as a readily accessible but imperfect surrogate for obesity. With only height and weight considered, BMI fails to capture the impact of central obesity on cardiovascular disease, diminishing its utility as a measure of obesity (101, 102). Indeed, studies have indicated that obesity, as represented by BMI, exhibits no significant association with AAA-related morbidity and is even inversely associated with AAA mortality (12, 87). However, when BMI is further dissected into fat and fat-free mass index, a negative correlation between fat-free mass and AAA morbidity emerges, highlighting the inadequacy of BMI alone in describing adipose tissue mass, distribution, and function (12). As the understanding of obesity deepens and imaging technology advances, more accurate measures of obesity have emerged, such as physical activity, physical activity, VAT area, PVAT density, and epicardial adipose tissue volume (EATV) (16, 103). Physical activity is known to improve cardiovascular health, reduce inflammation, and enhance metabolic profiles, all of which can positively impact the progression and management of AAA



(77). While physical activity contributes to maintaining a healthy weight and reducing visceral fat, studies have noted that accurately quantifying physical activity levels can be challenging, and self-reported activity may not always reflect true levels. Additionally, cardiorespiratory fitness (CRF) is frequently mentioned as an important metric for assessing obesity. CRF has been demonstrated to be a robust indicator of overall cardiovascular health and is often a better predictor of mortality and morbidity than BMI (104). High CRF levels are associated with improved vascular function, lower inflammation, and reduced cardiovascular risk. Visceral adipose tissue (VAT) and perivascular adipose tissue (PVAT) exert a greater and more direct impact on the cardiovascular system compared to subcutaneous adipose tissue, which has been shown to have minimal influence on cardiovascular disease (105). Future studies should aim to integrate these indices to evaluate their combined impact on the progression and management of AAA. This approach can help to identify at-risk individuals more accurately and develop tailored intervention strategies that address both weight management and overall cardiovascular fitness.

## 5 Weight loss and prehabilitation in AAA

It has been reported that severely obese patients undergoing AAA repair experience higher postoperative mortality, longer average hospital stays, and increased total hospital costs, primarily attributed to thromboembolism, wound infection, and renal complications (24, 106). Based on the modified Johns Hopkins surgical criteria, aortic surgery is considered high-risk with a cardiac risk exceeding 5% (107). During open aortic repair (OAR), excess fat can lead to challenges such as increased incision length, surgical dissection difficulty, prolonged surgery and anesthesia duration, and the need for postoperative ventilatory support, all of which elevate the risk of surgery and contribute to higher perioperative mortality (108). Although mortality rates do not increase with EVAR, severely obese patients face a higher risk of stroke and wound complications consistent with those observed in OAR (109). Furthermore, prolonged surgical incisions and excess fat can impede wound healing, potentially leading to graft infection, sepsis, and fatal outcomes (78).

Preoperative weight loss in severely obese patients has been shown to reduce perioperative risk. Similar to other cardiovascular diseases, moderate preoperative physical activity in AAA patients is beneficial, reducing the risk of cardiac, renal, and respiratory complications while maintaining safety (110, 111). Indeed, preoperative weight loss can be considered a form of prehabilitation, enhancing cardiopulmonary function reserve and positively impacting postoperative recovery. Studies have demonstrated that Angiotensin II-induced AAA mice fed a low-fat diet exhibit reduced abdominal aortic diameter and neovascularization compared to those fed a high-fat diet (112).

Moreover, a prospective randomized controlled trial involving 56 AAA patients revealed that participation in a community

exercise program significantly improved peak oxygen consumption (VO<sub>2</sub>) starting at week 16 and also enhanced triglyceride levels and health-related quality of life, significantly impacting perioperative mortality of AAA (113). Additionally, an interventional study involving 144 overweight and obese patients showed that weight loss induced by calorie restriction may reduce both thoracic and abdominal aortic diameters, although further investigation is required to ascertain their impact on AAA development prevention (114). However, a meta-analysis has indicated that prehabilitation exercise therapy may not reduce perioperative complications or length of hospital stay in AAA patients (115). This discrepancy could be attributed to the lack of separate comparisons among patients with different weight levels.

In addition to the aforementioned preoperative physical activity, medical interventions targeting severe obesity have been shown to reduce perioperative mortality in AAA. Several medical interventions aimed at treating obesity have shown promise in mitigating the progression of AAA. Pharmacological treatments, such as the use of statins, have been associated with both weight reduction and a decrease in the progression of AAA. Statins, known for their lipid-lowering effects, also possess anti-inflammatory properties that can help reduce the chronic inflammation associated with both obesity and AAA (116). Additionally, medications such as antihypertensives and antidiabetic agents may indirectly influence AAA progression by controlling blood pressure and glucose levels, thereby reducing vascular stress and inflammation (117). Despite substantial evidence indicating that bariatric surgeries, including gastric bypass and sleeve gastrectomy, can significantly reduce obesity-related perioperative mortality, there is a lack of specific reports on AAA, possibly due to issues related to the timing of surgery (118).

Building upon this understanding, we hypothesize that severe obese patients with AAA, who do not currently meet surgical criteria, can achieve a state of mild obesity through guided physical activity and diet control overseen by healthcare professionals. This approach could potentially reduce perioperative complications and delay the progression to surgical intervention, thus alleviating the economic burden on society.

Admittedly, this hypothesis warrants further investigation through both retrospective and prospective studies to assess its safety and feasibility. Such studies would provide valuable guidance in determining the efficacy and potential benefits of implementing physical activity and medical interventions in severe obese patients with AAA.

## 6 Discussion

This review comprehensively explores the relationship between obesity and AAA morbidity, perioperative mortality, and delves into the obesity paradox within AAA disease, analyzing its multifaceted causes. It emphasizes that both AAA and obesity are chronic aging diseases, shedding light on their intricate interplay. Furthermore, the review briefly discusses and looks ahead to the potential of preoperative prehabilitation for AAA patients.

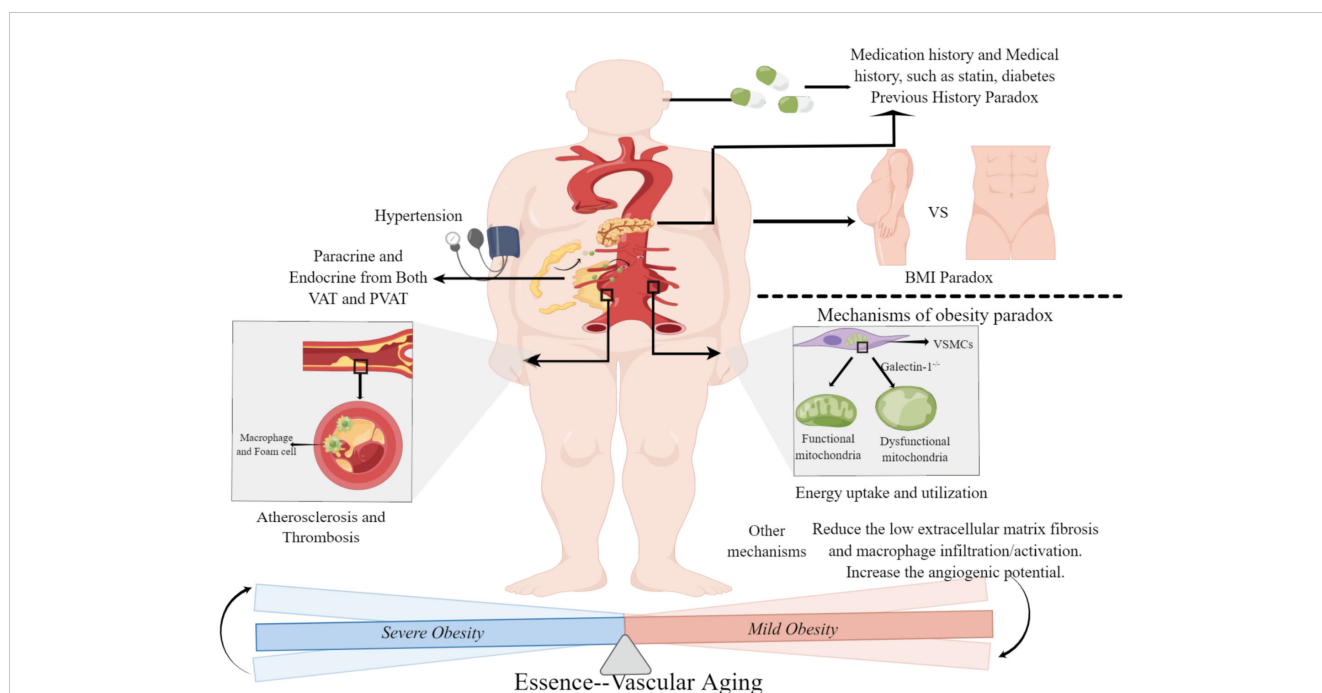
AAA has long been conceptualized as a manifestation of aortic aging, characterized by various histological changes. With advancing age, the aorta undergoes processes such as endothelial cell apoptosis, a switch in smooth muscle contraction phenotype, inflammation infiltration, and elastin degeneration (8, 119). At the cytological level, clinical studies have indicated decreased telomerase expression in the aortic endothelial nucleus of AAA patients compared to non-AAA individuals (120). Moreover, lysosome autophagy function is compromised in AAA. The TFEB gene, a crucial regulator of autophagy and lysosomal biogenesis, plays a pivotal role in maintaining cellular homeostasis. Experimental evidence has shown that TFEB gene knockdown in mouse VSMCs exacerbates the progression of experimental AAA (121).

In addition, several anti-aging drugs, including spermidine and polyunsaturated fatty acids, have demonstrated protective effects against the occurrence and progression of AAA in animal models by mitigating inflammatory infiltration, modulating autophagy, and preserving smooth muscle contraction phenotype (122, 123). However, randomized controlled clinical trials have yielded inconclusive results regarding the efficacy of polyunsaturated fatty acids in inhibiting or reversing the progression of AAAs. Despite their potential to improve the fatty acid profile and reduce vascular inflammatory infiltration and arterial stiffness in AAA patients, there remains insufficient evidence to support their role in halting or reversing AAA progression (124, 125).

Furthermore, adipocyte accumulation, particularly visceral fat associated with central obesity, contributes to systemic aging by promoting the secretion of inflammatory cytokines and altering the secretion of adipokines. This aging effect extends beyond blood vessels to affect other physiological systems, including the musculoskeletal and metabolic systems (126–128). Therefore, obesity can be viewed as a form of systemic aging.

Interestingly, the degree of obesity does not exhibit a linear correlation with perioperative mortality in AAA patients, despite representing systemic aging. This phenomenon, known as the obesity paradox, is not unique to AAA but is also observed in various other cardiovascular and non-cardiovascular diseases, such as coronary heart disease, cancer, and COPD (129–132). For instance, a randomized controlled clinical trial involving patients with hypertension and coronary heart disease revealed that individuals with a BMI of 25–30 kg/m<sup>2</sup> had the lowest perioperative risk and risk of death compared to normal-weight patients (131). Similarly, a meta-analysis involving patients with colorectal cancer demonstrated that overweight patients had better overall, disease-free, and cancer-specific survival than normal-weight patients (129).

The obesity paradox is predominantly observed in chronic diseases and is more prevalent among the elderly population. This phenomenon may stem from the complex interplay between chronic disease consumption and aging-related changes in the body, leading to decreased protein content, immune system



**FIGURE 2** Obesity paradox in abdominal aortic aneurysm. Severe obesity leads to a high morbidity and mortality of abdominal aortic aneurysm through the endocrine/paracrine function of adipose tissue and obesity-related comorbidities and complications. Mild obese patients with abdominal aortic aneurysm have a better prognosis, mainly because of improved energy uptake and utilization and regulation of the perivascular environment. The main difference between severe obesity and mild obesity is the degree of systemic aging, and the effect of obesity on abdominal aortic aneurysm is essentially the embodiment of systemic aging in vascular disease. BMI, Body Mass Index; VAT, Visceral Adipose Tissue; PVAT, Perivascular Adipose Tissue. (This figure is supported by Figdraw).

disorders, weakened resistance, and increased mortality (133, 134). Notably, observational studies have shown that malnutrition and cachexia result in poor long-term survival after EVAR despite reductions in total body fat (135–137). This suggests that the essence of the obesity paradox lies not solely in total body adipose content but in the overall aging condition of the body. Additionally, adipose tissue can serve as an energy source for chronic disease consumption in patients with poor general body condition, providing theoretical support for perioperative prehabilitation strategies.

While weight loss methods such as physical activity and medical interventions have demonstrated benefits in reducing abdominal aorta diameter and improving perioperative outcomes, there is currently insufficient high-level evidence to support its effectiveness in reducing perioperative complications of AAA. This lack of evidence is reflected in guidelines such as those from the National Institute for Health and Care Excellence (NICE) (9, 113, 115). Therefore, the appropriate population for prehabilitation interventions targeting weight loss in AAA patients requires further clarification.

Given the significant role of obesity in the development, progression, and treatment of abdominal aortic aneurysms (AAA), it is crucial to develop screening, monitoring, and intervention strategies tailored to the varying degrees of obesity in patients at risk for AAA. Firstly, current guidelines could be enhanced by incorporating obesity-specific risk factors, such as body mass index (BMI) and waist circumference, to identify high-risk individuals earlier. Advanced imaging techniques, such as ultrasound and CT angiography, should be considered for regular monitoring of obese patients with known AAA. Secondly, regular assessments of inflammatory markers (e.g., CRP, IL-6) and metabolic parameters (e.g., blood glucose, lipid profiles) can provide insights into the progression of AAA and the effectiveness of intervention strategies. Wearable technology and telemedicine can also play a role in improving the frequency and convenience of monitoring for patients. Lastly, medical interventions, such as the use of statins and antihypertensive drugs, can help control underlying risk factors. For patients with severe obesity, bariatric surgery should be considered not only for weight loss but also for its potential benefits in reducing perioperative risks and inflammation associated with AAA. Furthermore, lifestyle interventions, including diet and exercise programs, should be customized to ensure long-term adherence and effectiveness.

Additionally, the methods and strategies for achieving weight loss in patients with AAA need to be further explored. It is essential to strike a balance between reducing the risk of AAA rupture and facilitating rapid rehabilitation. This balance poses an urgent problem that needs to be addressed through continued research and clinical practice. Future studies should focus on identifying effective and safe approaches to weight loss in AAA patients and evaluating their impact on perioperative complications and overall outcomes. Moreover, individualized approaches considering the unique characteristics and needs of AAA patients may be necessary to optimize outcomes while minimizing risks (Figure 2).

## 7 Conclusions

In summary, severe obesity is associated with an increased risk of developing AAA and contributes to higher perioperative mortality, largely due to its complications and endocrine effects. Conversely, mild obesity appears to be protective against AAA mortality. While these observations may seem contradictory, they likely stem from factors such as measurement limitations and patients' medical histories. However, the notion of an obesity paradox in AAA is better understood as a reflection of systemic aging in abdominal aortic disease.

Furthermore, we discussed the significance of preoperative weight loss for severe obese patients with AAA, emphasizing the importance of timing and methodology in achieving optimal outcomes. Addressing obesity prior to surgery may help mitigate perioperative risks and improve overall prognosis. However, further research is needed to better understand the mechanisms underlying these relationships and to refine strategies for preoperative weight management in AAA patients.

## Author contributions

FL: Conceptualization, Data curation, Visualization, Writing – original draft, Writing – review & editing. YL: Conceptualization, Writing – original draft. JZ: Conceptualization, Data curation, Writing – review & editing. ZC: Conceptualization, Data curation, Writing – review & editing. YYL: Conceptualization, Data curation, Visualization, Writing – review & editing. MZ: Conceptualization, Data curation, Visualization, Writing – review & editing. LW: Conceptualization, Data curation, Funding acquisition, Supervision, Visualization, Writing – review & editing, Writing – original draft.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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