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Obesity and cardiovascular disease: revisiting an old relationship

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ABSTRACT

A wealth of clinical and epidemiological evidence has linked obesity to a broad spectrum of cardiovascular diseases (CVD) including coronary heart disease, heart failure, hypertension, stroke, atrial fibrillation and sudden cardiac death. Obesity can increase CVD morbidity and mortality directly and indirectly. Direct effects are mediated by obesity-induced structural and functional adaptations of the cardiovascular system to accommodate excess body weight, as well as by adipokine effects on inflammation and vascular homeostasis. Indirect effects are mediated by co-existing CVD risk factors such as insulin resistance, hyperglycemia, hypertension and dyslipidemia. Adipose tissue (AT) quality and functionality are more relevant aspects for cardiometabolic risk than its total amount. The consequences of maladaptive AT expansion in obesity are local and systemic: the local include inflammation, hypoxia, dysregulated adipokine secretion and impaired mitochondrial function; the systemic comprise insulin resistance, abnormal glucose/lipid metabolism, hypertension, a pro-inflammatory and prothrombotic state and endothelial dysfunction, all of which provide linking mechanisms for the association between obesity and CVD. The present narrative review summarizes the major pathophysiological links between obesity and CVD (traditional and novel concepts), analyses the heterogeneity of obesity-related cardiometabolic consequences, and provides an overview of the cardiovascular impact of weight loss interventions.

Contents

Abbreviations: AF, atrial fibrillation; AHA, American Heart Association; AMPK, adenosine monophosphate kinase; ANGPTL2, angiopoietin like protein 2; AT, adipose tissue; BMI, body mass index; BP, blood pressure; CAC, coronary artery calcification; CHD, coronary heart disease; CO, cardiac output; COPD, chronic obstructive pulmonary disease; CRF, cardiorespiratory fitness; CT, computed tomography; CVD, cardiovascular disease; EAT, epicardial adipose tissue; eNOS, endothelial nitric oxide synthetase; HF, heart failure; HR, heart rate; IL-6, interleukin 6; IL-10, interleukin 10; IL-18, interleukin 18; IMT, intima-media thickness; LA, left atrium; LV, left ventricle; MCP-1, monocyte chemoattractant protein 1; MHO, metabolically healthy obese; MRI, magnetic resonance imaging; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; NO, nitric oxide; NYHA, New York Heart Association; PAI-1, plasminogen activator inhibitor type 1; PASP, pulmonary artery systolic pressure; PVAT, perivascular adipose tissue; RBP-4, retinol binding protein 4; SAT, subcutaneous adipose tissue; SCD, sudden cardiac death; SFRP5, secreted frizzled-related protein 5; SOS, Swedish Obese Subjects; SV, stroke volume; SVR, systemic vascular resistance; T2DM, type 2 diabetes mellitus; TGF-β, transforming growth factor β; TNF-α, tumor necrosis factor α; VAT, visceral adipose tissue; WC, waist circumference; WHO, World Health Organization; WHR, waist-to-hip ratio; WHtR, waist-to-height ratio.

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1. Introduction

According to World Health Organization (WHO) estimates, over half of the global adult population is overweight or obese [1]. In many regions of the world, obesity prevalence is still increasing rapidly, and if the current trends continue, it will reach globally 18% in men and surpass 21% in women by 2025, imposing a heavy burden upon individuals, societies and health care systems [2]. Based on these data, obesity has been justifiably characterized as a modern global epidemic disease [3].

A wealth of clinical and epidemiological evidence has linked obesity to a broad spectrum of cardiovascular diseases (CVD) including coronary heart disease (CHD), heart failure (HF), hypertension, cerebrovascular disease, atrial fibrillation (AF), ventricular arrhythmias and sudden cardiac death (SCD). Obesity has been also linked to obstructive sleep apnea and other hypoventilation syndromes, which adversely affect cardiovascular function [4].

Obesity can increase CVD morbidity and mortality directly and indirectly. Direct effects are mediated by obesity-induced structural and functional adaptations of the cardiovascular system to accommodate excess body weight, as well as by adipokine effects on inflammation and vascular homeostasis, leading to a pro-inflammatory and pro-thrombotic milieu. Indirect effects are mediated by concomitant CVD risk factors such as insulin resistance, type 2 diabetes mellitus (T2DM), visceral adiposity, hypertension and dyslipidemia [5].

Body mass index (BMI), defined as body weight in kg divided by height in meters squared, is the most widely used anthropometric index to define obesity [6]. Although simple and reproducible, it has been heavily criticized for its intrinsic weakness to discriminate between fat and lean body mass and its inability to account for different patterns of body composition and regional fat distribution [7]. These limitations partly explain why concepts like the obesity paradox and the metabolically healthy obese (MHO) phenotype have raised scepticism and fuelled controversies in obesity research [8,9]. In support of the problematic use of BMI as an obesity index, various large-scale epidemiological studies including the case-control INTERHEART study, have shown that central adiposity is more strongly related to CVD risk than total adiposity expressed by BMI [10–12]. It has been therefore argued that anthropometric indices of central fat distribution such as waist circumference (WC), waist-to-hip ratio (WHR), waist-to-height ratio (WHtR) and imaging measurements of visceral fat by computed tomography (CT) or magnetic resonance imaging (MRI), should be assessed on top of BMI due to their better predictive power for CVD risk [13].

It has been further suggested that adipose tissue (AT) integrity and functionality are more relevant aspects for cardiometabolic risk determination than its total amount [14]. AT can regulate the fate of excess dietary lipids and determine whether metabolic homeostasis will be maintained or a state of low-grade systemic inflammation and insulin resistance will develop with deleterious cardiometabolic consequences. AT may also orchestrate interactions with other vital organs such as the brain, liver, skeletal muscle, heart and blood vessels within the framework of an inter-tissue metabolic cross-talk [15]. The consequences of AT expansion are both local and systemic: the local include inflammation [16], hypoxia [17], fibrosis [18], dysregulated adipokine secretion [19], and impaired mitochondrial function [20]; the systemic comprise insulin resistance, abnormal glucose and lipid metabolism, hypertension, a pro-inflammatory and pro-thrombotic state and endothelial dysfunction, all of which provide linking mechanisms between obesity and CVD [21].

The present narrative review summarizes the major pathophysiological links between obesity and CVD, analyses the heterogeneity of obesity-related cardiometabolic consequences, and provides an overview of the cardiovascular impact of weight loss interventions.

2. Epidemiological Evidence

The American Heart Association (AHA) has officially classified obesity as a major modifiable risk factor for CVD [22]. The relationship between obesity and CVD may be partly influenced by obesity-related comorbidities. There has been considerable debate as to whether it is necessary to adjust for these conditions in statistical models estimating the absolute CVD risk attributable to obesity, or whether such adjustments may actually inflate instead of control for the overall risk of bias [21]. In fact, the vast majority of epidemiological studies, including the Framingham Heart and Manitoba Study, conclude that obesity-associated CVD risk persists even after adjustment for co-existing risk factors, and therefore obesity is an independent CVD predictor [23–26].

Excess body weight and especially abdominal fat accumulation accelerate the progression of atherosclerosis decades before the first clinical manifestations of CHD, as shown in post-mortem studies in young individuals dying from non-CVD causes [27]. In these studies, the extent of fatty streaks and rupture-prone atherosclerotic plaques within the coronary arteries and aorta was associated with total and abdominal adiposity, independently of other risk factors (smoking, hypertension, hyperlipidemia, and diabetes) [28].

Approximately 11% of HF cases in men and 14% in women are attributable to obesity [26]. According to the Framingham Heart Study, each BMI increment by one unit is associated with a 5% increased HF risk in men and 7% in women, indicating a dose-dependent relationship [29]. Recent epidemiological data suggest that obesity is more strongly related to HF with preserved rather than reduced ejection fraction, particularly in women [30]. In a meta-analysis comparing new-onset HF between normal-weight and overweight subjects, being overweight increased the risk of developing HF by 33% [31].

Overall and visceral obesity are risk factors for cerebrovascular disease, independently of hypertension, hyperlipidemia and hyperglycemia. The Physicians' Health Study showed an increased risk for both ischemic and hemorrhagic stroke in obese patients [32]. The major underlying mechanisms include the increased prevalence of hypertension and AF, as well as a pro-thrombotic and pro-inflammatory state [33].

In the Framingham Heart Study, the annual rate of SCD was nearly 40-fold higher in obese subjects [34]. This is mainly attributed to increased cardiac electrical irritability, abnormal late potentials and disrupted sympathovagal balance, leading to more frequent and complex ventricular dysrhythmias, even in the absence of clinically overt HF [35]. Furthermore, obese patients have a nearly 50% increased risk of developing AF due to obesity-induced hemodynamic effects and the impact of obesity on cardiac structure and function [36].

3. Pathophysiological Links between Obesity and Cardiovascular Disease

3.1. Cardiovascular Adaptations to Obesity

Obesity induces adverse hemodynamic effects and a plethora of maladaptive modifications in cardiovascular structure and function. Major

Table 1
Obesity-induced hemodynamic effects and cardiovascular adaptations.

Hemodynamic and cardiac structural and functional adaptations associated with obesity
• ↑ Intravascular blood volume
• ↑ Stroke Volume (SV)
• ↑ Heart Rate (HR)
• ↓ Heart Rate Variability (HRV)
• ↑ Cardiac Output (CO)
• ↑ Systemic Vascular Resistance (SVR)
• ↑ Blood Pressure (BP)
• ↑ Pulmonary Artery Systolic Pressure (PASP)
• ↑ Filling pressures in left and right heart cavities
• LA enlargement
• LV dilatation
• LV hypertrophy (eccentric or concentric type)
• Abnormal LV diastolic filling

LA: left atrium; LV: left ventricle.

cardiac adaptations include [37]: increase in total circulating blood volume as a result of expanded intravascular volume due to sodium retention, increased cardiac output (CO) through an increase in stroke volume (SV) and a mild increase in heart rate (HR) due to sympathetic activation, in order to meet the metabolic demands of the enlarged adipose and lean tissue (CO=SVxHR), increased systemic vascular resistance (SVR) due to low-grade inflammation, hyperinsulinemia, sympathetic overactivity and sleep-disordered breathing [38]. As a result of increased CO and SVR, blood pressure (BP) is typically elevated (BP=COxSVR), leading to high rates of hypertension [39].

All these hemodynamic alterations, and mainly the increased total blood volume and CO, cause a shift of the Frank-Starling curve to the left due to increased filling pressures and volumes. This increases cardiac workload and predisposes obese individuals to an abnormal left ventricular (LV) geometry and adverse remodelling [37]. In detail, LV is progressively dilated to accommodate the increased venous return. In order to keep wall stress normal, eccentric [40] or concentric [41] LV hypertrophy may develop, leading to progressive diastolic and eventually systolic LV dysfunction. The left atrium (LA) is also influenced in obesity [42]. The increased circulating blood volume and abnormal LV diastolic filling [40] may lead to LA enlargement, raising the risk for HF and AF. The increased filling pressures in the right side of the heart may also lead to mild increases in pulmonary artery systolic pressure (PASP) in >50% of obese patients [43]. Table 1 summarizes the most representative obesity-induced hemodynamic effects and cardiovascular adaptations.

Not only overall adiposity, but also abnormal fat distribution and body composition may lead to adverse LV adaptations. In the Dallas Heart Study, visceral fat measured by MRI was associated with adverse LV remodelling [44]. In another cohort, skeletal muscle mass was positively associated with LV diastolic function, and the combination of excess visceral fat with reduced muscle mass was related synergistically to subclinical deterioration of LV structure and diastolic capacity [45].

The term obesity-associated cardiomyopathy or else *adipositas cordis* refers to the gradual replacement of the myocardium by irregular bands of AT, which can separate and cause pressure-induced atrophy of myocardial cells [46]. In conjunction with the toxic effects of locally produced adipokines on the adjacent myocardium, this fat infiltration may induce lipotoxicity and promote cardiomyocyte dysfunction. Histologically, cardiomyocyte hypertrophy, myocardial fat infiltration and fibrosis have been confirmed in post-mortem studies [47]. The clinical spectrum of obesity-associated cardiomyopathy may range from asymptomatic subclinical LV alterations to overt dilated cardiomyopathy [48]. Of note, subclinical changes in LV structure and function in asymptomatic obese patients can be identified years before clinically overt HF [49].

3.2. Adipose Tissue Dysfunction and the Role of Adipokines

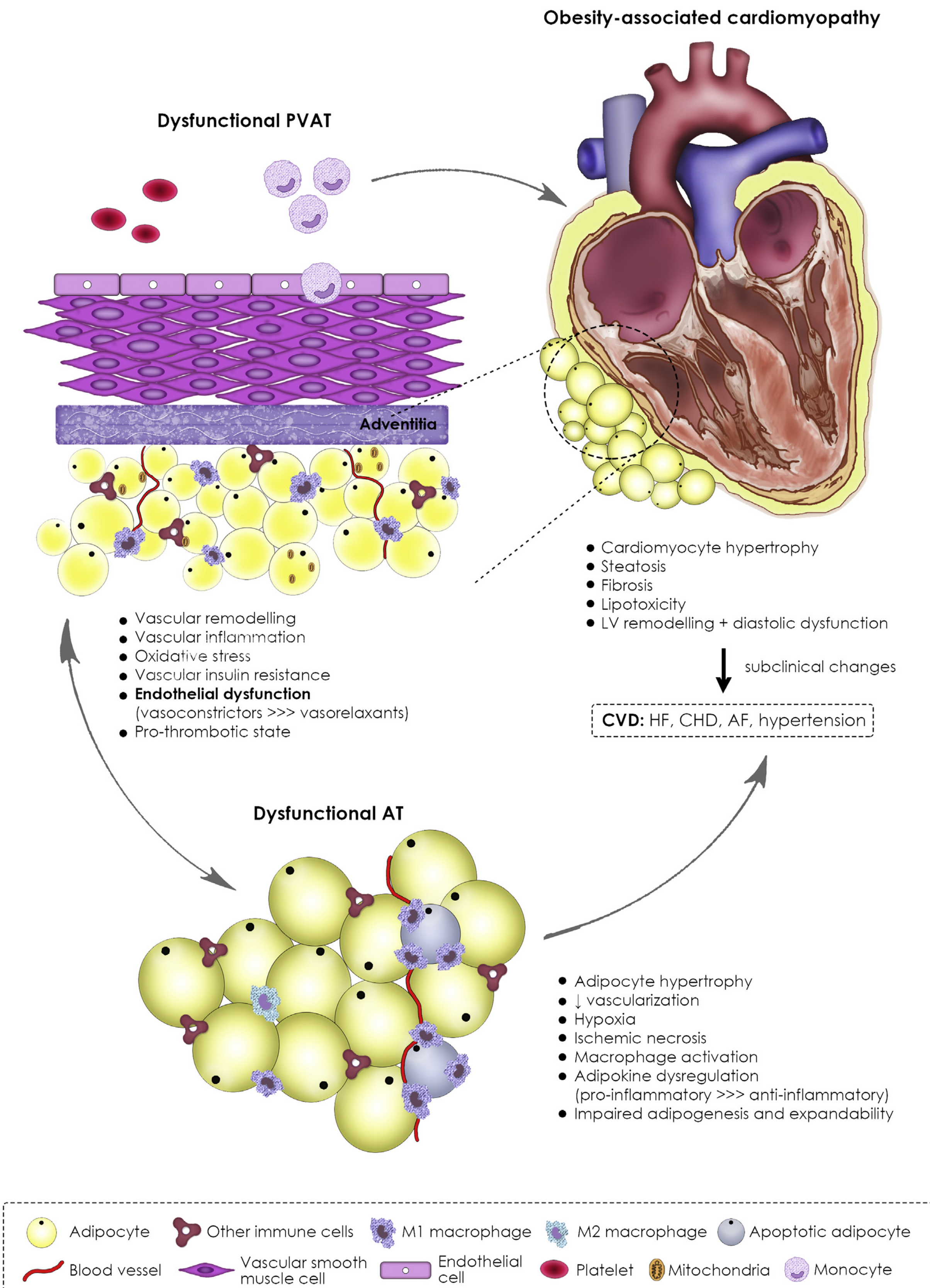
An overwhelming amount of research has clearly established that AT is not simply a passive storehouse for fat [50]. It has long been recognized as an active endocrine organ, able to synthesize and release into the circulation a variety of bioactive compounds (hormones, chemokines and cytokines), which are collectively termed adipokines and may act upon energy balance, immune responses, vascular homeostasis, angiogenesis, insulin sensitivity, glucose and lipid metabolism [51].

In obesity, AT undergoes a maladaptive expansion which may ultimately compromise its function. This is initially driven by adipocyte hyperplasia, mediated by the recruitment and proliferation of adipogenic precursors [52], followed by adipocyte hypertrophy [53]. The combined presence of hypertrophic adipocytes and decreased AT vascularization as a result of impaired angiogenesis and obesity-induced capillary rarefaction, promote localized hypoxia and ischemic necrosis, leading to necrotic and apoptotic adipocyte death [54]. This may in turn stimulate infiltration by activated macrophages and the initiation of a vicious cycle of inflammatory response [55]. AT expansion is associated with a number of qualitative and quantitative changes in the composition and phenotype of its cells [56]. Obesity promotes the polarization of resident AT macrophages toward a pro-inflammatory phenotype (M1-polarized), which can activate inflammatory pathways and impair insulin signalling [57]. The complex interactions between different cell types within the enlarged and inflamed AT may contribute to its overall impact on obesity-related complications.

Adipokines are considered to be at the crossroads between obesity and CVD [58]. Adipokine dysregulation, defined as an imbalance between pro- and anti-inflammatory compounds in favor of the pro-inflammatory ones, is a prominent hallmark of dysfunctional AT [58]. Under conditions of normal energy balance, adipocytes predominantly secrete anti-inflammatory adipokines such as adiponectin, transforming growth factor β (TGF-β), interleukin 10 (IL-10), secreted frizzled-related protein 5 (SFRP5) and nitric oxide (NO), which promote insulin sensitivity and exert cardioprotective and anti-atherogenic effects [59]. In contrast, dysfunctional hypertrophic adipocytes in the setting of sustained exposure to excess dietary fat predominantly produce and release pro-inflammatory adipokines such as leptin, tumor necrosis factor α (TNF-α), interleukin 6 (IL-6), interleukin 18 (IL-18), resistin, retinol binding protein 4 (RBP-4), lipocalin 2, and angiopoietin-like protein 2 (ANGPTL2), which exert atherogenic effects [60]. Hyperleptinemia, as a result of both excess AT and hypothalamic leptin resistance, has been associated with adverse CVD outcomes through vascular inflammation, oxidative stress, atherothrombosis, LV hypertrophy and systemic insulin resistance [61]. Adiponectin is considered a fundamental anti-atherogenic adipokine [62]. It inhibits the transformation of macrophages into foam cells within atherosclerotic plaques [58], and exerts vasculoprotective effects by

Fig. 1. The pathogenetic role of AT and PVAT dysfunction in the development of obesity-associated cardiomyopathy and CVD. Under conditions of positive energy balance, AT becomes expanded and dysfunctional. The combination of adipocyte hypertrophy and reduced AT vascularization leads to local hypoxia and apoptotic death of adipocytes, which stimulates the recruitment of activated macrophages and the initiation of a vicious pro-inflammatory cycle. This is histologically manifested as the so-called crown-like structures, which represent activated M1 macrophages surrounding apoptotic adipocytes. A prominent hallmark of dysfunctional AT is adipokine dysregulation, namely an imbalanced secretion of pro- and anti-inflammatory adipokines in favor of the pro-inflammatory ones. An abnormal fat depot with particularly relevant implications for CVD is PVAT, namely adventitial fat around the major coronary arteries within epicardial AT, which may directly affect cardiovascular structure and function. In obesity, PVAT is dysfunctional. PVAT dysfunction is associated with vascular remodelling, inflammation, oxidative stress, insulin resistance and endothelial dysfunction expressed as an imbalance between vasorelaxant and vasoconstrictor factors in favor of the vasoconstrictors. All these factors lead to maladaptive structural and functional alterations of the heart such as LV remodelling and diastolic dysfunction, sometimes termed obesity-associated cardiomyopathy, and through a period of asymptomatic subclinical disease, may ultimately result in clinically overt CVD, including CHD, HF, hypertension and arrhythmias. AF: atrial fibrillation; AT: adipose tissue; CHD: coronary heart disease; CVD: cardiovascular disease; HF: heart failure; LV: left ventricular; PVAT: perivascular adipose tissue.

improving endothelial function as a result of increased NO production through AMPK (adenosine monophosphate kinase)-dependent activation of endothelial NO synthetase (eNOS) [63]. Another emerging field of investigation is the role of plasma endocannabinoids such as anandamide and 2-arachidonoylglycerol, which are released from AT and have been linked to a number of obesity-related complications such as nephropathy, atherosclerosis and cardiovascular dysfunction [64]. Endocannabinoids are increased in obesity as a result of insulin resistance,



inflammation and oxidative stress, and may stimulate cannabinoid receptors and contribute to excess visceral fat and reduced adiponectin levels [64].

Notably, the pathogenetic links between adipokines and obesity-related CVD are difficult to disentangle, considering the large number of AT-derived secretory products and their complex interactions. Furthermore, it is not easy to discern whether the adverse CVD outcomes associated with the obesity-induced adipokine imbalance are mainly driven by paracrine effects, or predominantly influenced by endocrine mechanisms, as reflected by increased circulating adipokine levels [58].

3.3. Regional Fat Distribution and Abnormal Fat Depots

Pioneer studies in the USA and Sweden in the early 1980s showed that body shape is more important than size in predicting cardiometabolic outcomes [65,66]. AT is dispersed throughout the body in discrete depots ranging from 5 to 60% of total body weight [67]. More than 80% is found subcutaneously, mainly in the abdominal and gluteofemoral regions. Visceral adipose tissue (VAT) represents the remaining 10–20% of total body fat in men, and 5–10% in women [68]. Compelling evidence has established a strong link between visceral obesity and a constellation of risk factors such as insulin resistance, atherogenic dyslipidemia, hypertension and increased overall CVD risk [69]. In contrast, peripheral fat deposition has a favorable impact on CVD risk [70].

In the setting of positive energy balance, excess energy should be channelled into the insulin sensitive subcutaneous AT (SAT), which expands through hyperplasia, in order to prevent fat spillover to other compartments [71]. If SAT is absent, saturated by fat, dysfunctional or insulin resistant, the triglyceride surplus will be inevitably deposited in abnormal sites where fat accumulation is usually minimal, such as the liver, pancreas, heart, skeletal muscle and visceral depots, predisposing to cardiometabolic dysregulation [71]. Excessive intra-organ and peri-organ fat deposition has been pathogenetically associated with insulin resistance, systemic inflammation and cardiovascular dysfunction [72]. Conversely, preferential fat storage in the lower body (peripheral adiposity) may act as a metabolic "sink" and protect vital tissues from the deleterious effects of lipotoxicity caused by lipid overflow [71].

An abnormal fat depot with special implications for CVD lies around the heart, and has been consistently related to CVD risk [73–75]. Cardiac fat depots are classified into intramyocardial fat within cardiomyocytes, epicardial fat on the surface of the myocardium, pericardial fat located between the parietal and visceral pericardium, and paracardial fat located outside the pericardium [76]. Within epicardial fat, AT surrounding the major conduit coronary arteries is termed perivascular adipose tissue (PVAT) and has emerged as a major contributor to CVD risk [77,78], with similar pathophysiological implications as visceral fat.

PVAT provides structural and mechanical support to the underlying vasculature, but also influences vascular function by releasing a large number of vasoactive factors with paracrine effects, which target vascular smooth muscle and endothelial cells, regulating vascular tone, blood flow distribution, angiogenesis, inflammatory processes and endothelial function [21]. PVAT secretes leptin, adiponectin, resistin, visfatin, chemerin, TNF-α, IL-6, IL-18, monocyte chemoattractant protein 1 (MCP-1) and plasminogen activator inhibitor type 1 (PAI-1), all of which may modulate vascular tone, smooth muscle cell migration and proliferation, neointimal formation, inflammation and oxidative stress [79–82]. Chemerin has been recognized as a potent endogenous mediator of vasoconstriction in obesity, with additional pro-apoptotic, pro-inflammatory and proliferative effects on vascular cells [83]. The exact mechanisms by which these vasoactive factors are delivered from adventitial fat to coronary endothelium and vascular smooth muscle cells warrants further investigation. In obesity, PVAT becomes enlarged and dysfunctional, leading to an imbalance between vasorelaxant and vasoconstrictor factors in favor of vasoconstrictor and pro-inflammatory ones [84]. PVAT dysfunction is associated with adverse vascular remodelling, vascular inflammation, oxidative stress and insulin resistance, leading to decreased NO bioavailability [85]. PVAT thickness around the coronary arteries has been associated with indices of total and visceral adiposity and cardiometabolic parameters [86]. Fig. 1 illustrates the crucial pathogenetic role of dysfunctional AT and PVAT in obesity-associated cardiac abnormalities and clinically overt CVD.

Other abnormal fat depots with special CVD implications include intrahepatic, epicardial and peri-renal fat [72].

3.4. Non-alcoholic Fatty Liver Disease (NAFLD)

NAFLD is associated with increased CVD incidence and mortality [87], and CVD represents the major cause of death among NAFLD patients [88]. NAFLD may independently predict CVD risk, and non-alcoholic steatohepatitis (NASH) has been proposed as an equivalent of CHD. Obesity-associated insulin resistance is thought to be the predominant driver of both the initial intra-hepatic fat accumulation and the subsequent progression of steatosis to NASH, cirrhosis and hepatocellular carcinoma [89]. NAFLD has been pathogenetically linked to microvascular dysfunction, coronary artery atherosclerosis, inflammation and numerous traditional CVD risk factors comprising obesity, insulin resistance, hypertension and atherogenic dyslipidemia (including post-prandial lipemia) [90]. It has been also epidemiologically linked to an increased risk of AF [91]. Statins have been reported to improve both biochemical and histological features of NAFLD, while pioglitazone and ezetimibe may also exert beneficial effects [88]. Most studies emphasize the need for a multifactorial treatment, based upon lifestyle modification, hypolipidemic and hypoglycemic drugs [72].

3.5. Epicardial Fat

Epicardial adipose tissue (EAT) is considered to be crucial for the development of obesity-related cardiovascular complications. EAT-derived cytokines, adipokines and reactive oxygen species may favor the development of a local pro-atherogenic milieu by paracrine and vasocrine mechanisms, thus promoting the pathogenesis of CHD and cardiac arrhythmias [92]. Furthermore, EAT may predispose to AF *via* effects upon structural and electrical remodelling of the myocardium. In small amounts, EAT exerts anti-atherogenic and cardioprotective effects. However, excess EAT in the context of cardiometabolic disorders is only detrimental. Excess EAT has been related to abnormal myocardial flow reserve, coronary plaque vulnerability, coronary artery calcification, as well as the presence and severity of CHD [72]. Its thickness can be measured with ultrasound, CT and MRI. Lifestyle interventions, liraglutide and statins have been reported to decrease EAT volume and thus confer cardiometabolic benefits [72].

3.6. Peri-renal Fat

This extra-peritoneal fat layer surrounding the kidneys can be measured by ultrasound and CT, and has been associated with visceral adiposity, microalbuminuria, hypertension and overall kidney dysfunction in patients with T2DM [72].

3.7. The Emerging Role of Gut Microbiota

An aberrant composition of gut microbiota and altered levels of gut-derived peptides in response to a high-fat diet have been recognized as an early event in the initiation of systemic low-grade inflammation that may precede obesity [93]. The most common changes associated with obesity include a decrease in the ratio of Gram(+) Firmicutes to Gram (−) Bacteroidetes, and an abundance or depletion of certain species [94]. These changes seem to lead to an upregulation of inflammatory pathways and increased intestinal permeability. Accumulating evidence has unravelled an interconnection between intestinal bacteria-mediated inflammation, AT and skeletal muscle in a coordinated circuitry favoring the onset of high-fat diet-related systemic inflammation and predisposing to elevated cardiometabolic risk [93]. Although gut microbiota seems a key pathophysiological player for many disease states, the causality of this relationship has not been conclusively established, since it is not clear whether microbiota changes are the cause or rather the consequence of disease.

4. Cardiovascular and Metabolic Heterogeneity of Obesity

BMI-defined obesity is a remarkably heterogeneous condition with varying cardiometabolic risk across individuals with similar BMI [69]. Part of this variability is attributed to different patterns of fat distribution and the intrinsic properties of regional fat depots, including their developmental origin, adipogenic and proliferative capacity, insulin sensitivity, hormonal control, thermogenic ability and vascularization [21]. This cardiometabolic heterogeneity becomes particularly evident when studying the concepts of the obesity paradox and MHO.

4.1. The Obesity Paradox Hypothesis

According to this hypothesis, overweight and obese patients with established CVD display lower mortality than normal-weight patients [95]. This paradoxically protective effect on all-cause and CVD mortality has been reported in a broad spectrum of CVD, including CHD [96], HF [97], hypertension and AF [95]. Among CVD manifestations, advanced HF, especially its non-ischemic type, has been particularly associated with the obesity paradox phenomenon [98–100]. Beyond CVD, the paradox has been described in other chronic disease populations such as end-stage renal disease, advanced malignancies, chronic obstructive pulmonary disease (COPD), and rheumatoid arthritis [95]. The paradox seems to be evident in overweight (BMI: 25–30 kg/m^2) and mildly obese patients (BMI: 30–35 kg/m^2) [98]. In contrast, patients with grade II and III adiposity (BMI: >35 kg/m^2) display increased mortality and poorer prognosis [101]. Therefore, the term BMI paradox might be more accurate for these epidemiological findings, especially in light of observations that central obesity defined by WC and WHR is positively associated with increased mortality in patients with CHD [102].

Age-related changes in fat distribution and body composition, especially reduced muscle mass (sarcopenia), may partly explain the obesity paradox, since it is usually observed in frail elderly patients [103]. The following arguments have been proposed to explain the paradoxically protective effects of excess adiposity in CVD and especially HF [104]: (i) obese patients with HF may have more metabolic reserves to confront the catabolic state of advanced HF [105], (ii) the cytokine and neuroendocrine profiles of obese patients with CVD may be protective [97], (iii) AT secretes soluble TNF-α receptors which may protect obese patients by neutralizing the detrimental effects of circulating TNF-α [106], (iv) obese patients with HF have lower circulating atrial natriuretic peptide levels [107] and may also display attenuated renin-angiotensin responses [97], (v) obese patients may tolerate higher doses of cardioprotective BP-lowering medications due to higher baseline BP [97], (vi) higher circulating lipoproteins in obese patients may bind and detoxify lipopolysaccharides and prevent the endotoxin-mediated pro-inflammatory cascade [108].

Opponents of the theory emphasize that it does not reflect a true survival advantage, but rather the effect of confounding and multiple biases influencing the association of obesity with CVD, including smoking, physical activity and overall health status [109,110]. After adjusting for these confounders by excluding smokers and patients with comorbidities or prior CVD, and controlling for reverse causality by omitting the first year(s) of follow-up, the paradox disappears, and overweight/obese patients present an increased rather than decreased all-cause mortality [111,112]. In a recent large epidemiological study of healthy middle-aged UK subjects, the observed J-shaped relationship between BMI and CVD was significantly attenuated when participants with comorbidities were excluded or only non-smokers were analysed [113]. In contrast, the associations of other adiposity measures such as % body fat, WC, WHR and WHtR with CVD incidence/mortality were more linear and less susceptible to confounding [113]. Another important factor is the remarkable selection bias [14]. Lean subjects who develop CHD are likely to have a genetically-determined susceptibility to CHD, compared with those who develop CHD because of adiposity. This means that obese patients might be less prone to CHD recurrence. Another bias may be associated with the timing of weight measurement [103]. Some patients experience spontaneous weight loss after the diagnosis of HF (cardiac cachexia), making it difficult to discern whether pre-existing obesity drives the protective effects, or unintentional weight loss after diagnosis impacts negatively upon prognosis. It has been further suggested that cardiorespiratory fitness (CRF) is a more important determinant of survival in CVD patients than weight [114]. CRF interacts with and modulates the obesity paradox phenomenon in patients with HF and CHD [115]; the paradox appears to be limited to unfit individuals, and is substantially attenuated in patients with high CRF levels [116].

Table 2 summarizes the major arguments for and against the obesity paradox theory. All arguments considered, it seems more a misconception than a clinically meaningful relationship.

4.2. The Metabolically Healthy Obese Phenotype

The MHO phenotype was first described in the 1980s, but the major advancements in its characterization have been made since 2000, with the use of transgenic animal models, sophisticated imaging techniques for body composition analysis, and *in vivo* measurements of insulin sensitivity [117]. MHO prevalence varies depending on population and diagnostic criteria [9]. The lack of a standardized MHO definition has been the major obstacle in understanding the nature of this phenotype and its associated long-term health risks [117].

MHO individuals are characterized by increased insulin sensitivity for the degree of their adiposity, decreased visceral and liver fat, healthy AT expansion associated with a favorable adipokine profile, reduced inflammation, improved postprandial metabolism as suggested by meal-stimulated incretin responses, normal lipid profile, favorable lipidomic and metagenomic signatures, increased CRF, enhanced mitochondrial function and metabolic flexibility [117,118].

Initially, the MHO phenotype was believed not to be associated with increased CVD morbidity and mortality compared with normal-weight [119]. However, recent long-term studies and meta-analyses have provided robust evidence that MHO is not a benign condition [120,121]. It is associated with subclinical target organ damage, including increased carotid intima-media thickness (IMT) [122], coronary artery calcification [123], subtle impairment of LV structure and function [124] and impaired vasoreactivity [125]. Furthermore, MHO appears to be a transient metabolic state, since these subjects convert to an unhealthy phenotype more frequently and rapidly than their non-obese counterparts (65% conversion rate in 10 years) [126]. Independent predictors of this conversion include visceral fat accumulation, hyperinsulinemia, low levels of high-density lipoprotein cholesterol and female sex [126]. MHO subjects also display an increased risk of diabetes, chronic kidney disease, CVD and all-cause mortality in the long term [9,127]. It is therefore necessary to prospectively follow-up these subjects in order to detect long-term CVD risks. Although it seems that MHO is associated with increased mortality regardless of the definition [128], divergent definitions make the comparison of prevalence and outcomes between different studies challenging [129]. It is therefore essential to agree upon a universally accepted definition for metabolic health and obesity [9].

The rationale for investing research into this phenotype was driven by the need to provide clinical risk stratification among obese individuals, and to prioritize treatment for those who need it most urgently. On the other hand, by labelling a subset of obese people as MHO, physicians may show inertia in treating people with increased CVD risk [98,130]. It has been argued that an effective strategy would be to target transitioning from an unhealthy to a healthy cardiometabolic phenotype, without necessarily aiming at profound weight loss [131]. However, high-quality evidence for this recommendation is lacking.

Table 2
Arguments for and against the obesity paradox hypothesis.

For	Against
• Better metabolic reserve due to excess body fat	• Selection bias
• Protective cytokine and neuroendocrine profiles	• Regression dilution bias related to measurement error
• AT secretion of soluble TNF-α receptors neutralizing the effects of circulating TNF-α	• Bias related to the timing of weight measurement
• Lower atrial natriuretic peptide levels	• Reverse causality
• Attenuated renin-angiotensin response	• Confounding of smoking
• Tolerability of higher doses of antihypertensive medications with cardioprotective effects	• Confounding of comorbidities and overall health status
• Endotoxin detoxification due to increased circulating lipoproteins	• Confounding of CRF
	• Role of fat distribution

AT: adipose tissue; CRF: cardiorespiratory fitness; TNF-α: tumor necrosis factor α.

5. Cardiovascular Impact of Weight Loss Interventions

The controversy surrounding the obesity paradox has raised the intriguing question whether purposeful weight loss in patients with established CVD may be beneficial or harmful [95]. In terms of body composition, preferential loss of body fat without losing lean body mass seems to be beneficial, and associated with lower mortality in obese patients with CVD [132,133].

According to a recent meta-analysis, low-fat weight loss diets are associated with reduced all-cause mortality, but have no significant impact on CVD incidence and mortality in obese adults [134]. Among patients with already established CVD, the most effective strategy to reverse obesity-associated CVD risk factors is thought to be dietary modification combined with structured exercise programs, termed as cardiac rehabilitation [135].

In obese patients with CHD, a 5–10% weight loss through cardiac rehabilitation enhanced CRF, improved plasma lipids and glucose levels, reduced serum inflammatory markers, and tended to reduce mortality [136–138]. In another study in CHD patients, intentional weight loss was beneficial for CVD morbidity/mortality in both obese and non-obese patients [139].

Weight reduction may also have a positive impact on LV structure and function. A loss of 8 kg reduced LV wall thickness in mildly obese hypertensive patients, and performed better than standard pharmacologic treatment [140]. In morbidly obese patients with HF achieving drastic weight loss after bariatric surgery, New York Heart Association (NYHA) functional class improved in nearly all patients [141].

Among all weight loss interventions, bariatric surgery has yielded unequivocal beneficial effects on short-and long-term CVD morbidity and mortality [142–144]. The Swedish Obese Subjects (SOS) study has shown that diabetes, dyslipidemia and hypertension remission is higher, and their incidence lower 10 years after surgery, compared with the control group [145]. The resolution rate for dyslipidemia was reported to be 73–80%, and for hypertension 62% over at least 6 years post-operatively [146]. Bariatric surgery is also associated with a reduction of CVD incidence by 33% [147]. Beyond traditional CVD risk factor amelioration, it has been shown to improve many cardiovascular indices including heart rate variability, EAT thickness and LV performance [148], and furthermore reduce markers of systemic inflammation [149].

6. Cardiovascular Effects of Anti-Obesity Pharmacotherapy

Anti-obesity medications have been plagued in the past by high rates of CVD adverse effects. Agents withdrawn from the market due to unexpected CVD side effects include fenfluramine/dexfenfluramine (valvular abnormalities), sibutramine (HR, BP and CVD event increases), ephedrine (sympathetic activation and thermodysregulation), and phenylpropanolamine (hemorrhagic stroke) [150]. Rimonabant was withdrawn due to neuropsychiatric side effects. Orlistat, for years the only approved weight loss medication, has a relatively favorable CVD safety profile [150]. The phentermine/topiramate combination (sympathomimetic plus antiepileptic), approved by the FDA in 2012, is not recommended in patients with high CVD risk due to increased rates of tachycardia and palpitations and lack of robust long-term CVD safety data [150]. Lorcaserin, a selective serotonin 2c receptor agonist also approved in 2012 by the FDA, was recently found to exhibit a cardiovascular safety profile comparable to placebo in overweight and obese patients with high CVD risk during a median follow-up of 3.3 years [151]. However, the numerical excess of lorcaserin-associated valvulopathy cases underlines the need for longer-term safety studies. The novel sustained-release combination of naltrexone (opioid antagonist) and bupropion (antidepressant), approved by both the FDA and EMA, has been associated with an improved lipid profile and a reduction of inflammatory biomarkers, but also with transient increases in BP, thus prompting further investigation of its CVD safety [150]. In view of the unexpected early termination of a randomized clinical trial assessing major adverse CVD events in high-risk obese patients receiving naltrexone/bupropion, the cardiovascular safety of this treatment remains uncertain [152].

Recently, glucose-lowering medications which are increasingly prescribed in patients with T2DM, namely liraglutide (glucagon-like peptide 1-receptor agonist) and the sodium/glucose cotransporter 2 inhibitors empagliflozin and canagliflozin, have shown the potential to induce weight loss and reduce CVD morbidity and mortality [153–155]. Liraglutide is now approved by both the FDA and EMA for the treatment of obesity in the absence of T2DM, and the once weekly GLP-1 analogue semaglutide, approved for the treatment of T2DM and currently extensively studied in phase III clinical trials as an anti-obesity medication, has also shown favorable cardiovascular effects in patients with T2DM [156]. Liraglutide in particular has been shown to decrease liver fat content and induce histological resolution of biopsy-proven NASH in a phase II study [157], as well as induce a large and rapid reduction of EAT thickness in T2DM patients [158].

Although the currently approved weight loss medications may improve a number of CVD risk factors, data on hard endpoints such as the actual reduction of clinical CVD events are limited. Long-term CVD outcome studies are thus urgently needed.

7. Summary and Conclusions

Obesity is linked to a broad spectrum of CVD including CHD, HF, hypertension, stroke, AF, ventricular arrhythmias and SCD, independently of concomitant risk factors. AT has long been recognized as an active endocrine organ, able to synthesize and release a variety of bioactive molecules, collectively termed adipokines. Adipokines are at the crossroads between obesity and CVD, and their dysregulation is a prominent hallmark of dysfunctional AT in obesity. Regional fat distribution, the size of each fat depot and the depot-related differences in AT function are important determinants of individual cardiometabolic risk. An abnormal fat depot with particularly relevant implications for CVD is PVAT, adventitial fat around the major coronary arteries, which directly affects cardiovascular function. In obesity, PVAT is linked to vascular remodelling, inflammation, oxidative stress, insulin resistance and endothelial dysfunction. BMI-defined obesity is heterogeneous in terms of cardiometabolic risk, mainly because of different patterns of fat distribution and the intrinsic properties of distinct fat depots. This heterogeneity is particularly evident in the concepts of the obesity paradox and MHO. The obesity paradox appears to be more a misconception, while the concept of MHO is also controversial, but provides the opportunity to investigate the biological causes and consequences of health heterogeneity among people with similar BMI. Intentional weight reduction is beneficial for CVD morbidity and mortality in obese patients, and may have a positive impact on LV structure and function, especially preferential loss of fat mass. Bariatric surgery leads to substantial cardiovascular benefits. Some of the currently approved weight loss medications have pleiotropic actions and may improve several CVD risk factors. Nevertheless, data on hard endpoints are scarce and long-term CVD outcome studies in high-risk patients are needed.

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Conflict of Interest Statement

The authors declare no conflict of interest.

Authors' Contributions

C.K. reviewed the literature and drafted the manuscript; S.L. edited and critically reviewed the manuscript; A.K. conceived the outline, coordinated writing and provided critical review. All authors approved the final version of the manuscript.

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