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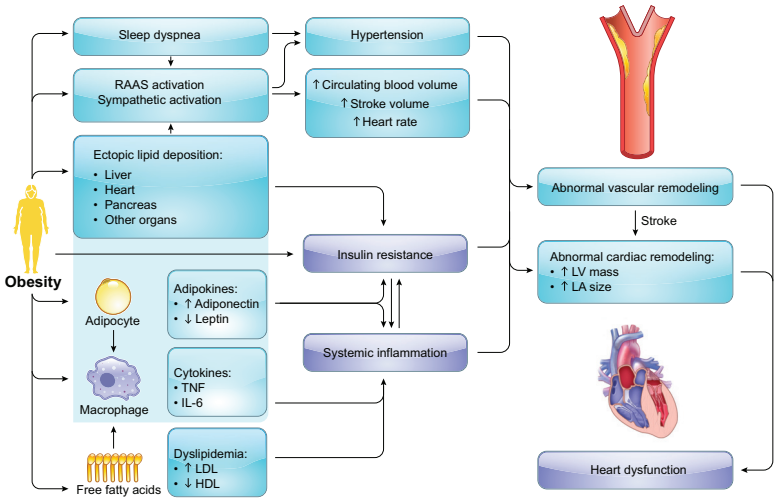
OBESITY CARDIOMYOPATHY: EVIDENCE, MECHANISMS, AND THERAPEUTIC IMPLICATIONS



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KEY WORDS

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CLINICAL HIGHLIGHTS

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OBESITY CARDIOMYOPATHY: EVIDENCE, MECHANISMS, AND THERAPEUTIC IMPLICATIONS

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Abstract

The prevalence of heart failure is on the rise and imposes a major health threat, in part, due to the rapidly increased prevalence of overweight and obesity. To this point, epidemiological, clinical, and experimental evidence supports the existence of a unique disease entity termed "obesity cardiomyopathy," which develops independent of hypertension, coronary heart disease, and other heart diseases. Our contemporary review evaluates the evidence for this pathological condition, examines putative responsible mechanisms, and discusses therapeutic options for this disorder. Clinical findings have consolidated the presence of left ventricular dysfunction in obesity. Experimental investigations have uncovered pathophysiological changes in myocardial structure and function in genetically predisposed and diet-induced obesity. Indeed, contemporary evidence consolidates a wide array of cellular and molecular mechanisms underlying the etiology of obesity cardiomyopathy including adipose tissue dysfunction, systemic inflammation, metabolic disturbances (insulin resistance, abnormal glucose transport, spillover of free fatty acids, lipotoxicity, and amino acid derangement), altered intracellular especially mitochondrial Ca^{2+} homeostasis, oxidative stress, autophagy/mitophagy defect, myocardial fibrosis, dampened coronary flow reserve, coronary microvascular disease (microangiopathy), and endothelial impairment. Given the important role of obesity in the increased risk of heart failure, especially that with preserved systolic function and the recent rises in COVID-19-associated cardiovascular mortality, this review should provide compelling evidence for the presence of obesity cardiomyopathy, independent of various comorbid conditions, underlying mechanisms, and offer new insights into potential therapeutic approaches (pharmacological and lifestyle modification) for the clinical management of obesity cardiomyopathy.

cardiovascular disease; glucotoxicity; heart; inflammation; lipotoxicity; obesity; therapy

1. INTRODUCTION (OVERVIEW OF OBESITY)

1.1. *Facts about Prevalence and Health Consequences of Obesity*

1.1.1. Epidemiology of obesity.

The World Health Organization (WHO) defines overweight and obesity as a pathological setting with abnormal or excessive fat accumulation. Obesity is generally rooted in a complex interplay between genetic and environmental factors such as culture, socioeconomical status, and lifestyle, leading to an alarming health concern in the 21st century (1–7) (see BOX 1). Body mass index (BMI), estimated by body weight in kilograms divided by the square of height in meters, is the simplest index employed to categorize overweight and obesity in adults. Current guidelines from the US Centers for Disease Control and Prevention and the WHO classify a healthy BMI in the window of 18.5–24.9, whereas a BMI $\geq$25 kg/m^2 is classified as overweight, and a BMI $\geq$30 kg/m^2 is deemed obese, with severe obesity (morbid obesity) listed as a BMI $\geq$40 kg/m^2 (5, 8, 9). Over the past two decades, the worldwide prevalence of overweight and obesity has risen dramatically, mainly driven by socioeconomical and lifestyle changes manifested by lower energy expenditure (physical activity) and increased usage of energy-rich food sources, especially refined carbohydrates (1, 5, 6). Uncorrected obesity unfavorably impacts all aspects of physiological functions, lowers quality of life, and increases the risk of illness and healthcare burden worldwide (1, 7, 10). This review will discuss

*J. Ren, N. N. Wu, and S. Wang contributed equally to this work.

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current contemporary knowledge of the causes and underlying mechanisms in adiposity and associated cardiovascular disease (CVD), with an ultimate aim to offer guidance for more effective and targeted antiobesity therapy in particular obesity-induced cardiac anomalies.

1.1.1.1. GLOBAL EPIDEMIOLOGY. According to the WHO, the overall prevalence of obesity has doubled in the United States and in most of the Westernized countries since 1980 and nearly tripled worldwide between 1975 and 2016 (4, 11, 12). A total of 1.9 billion individuals were classified to be overweight and 650 million adults presented obesity in 2016, representing 39% and 13%, respectively, of world population (3). Specifically, 39% of adults, including 39% of men and 40% of women, met the criteria of overweight and 13% of adults, including 11% of men and 15% of women, reached the threshold of obesity in 2016 (**FIGURE 1**). The age-justified prevalence of overweight and obesity rose by almost 50% (26.5% in 1980 to 39.0% in 2015) and 80% (7% in 1980 to 12.5% in 2015), respectively (3). In another independent report, the prevalence of obesity jumped from 3.2% to 10.8% in adult men and 6.4% to 14.9% in adult women between 1975 and 2014. In 2014, 0.64% of men and 1.6% of women exhibited morbid obesity (BMI $\geq$40) (1). More alarmingly, the prevalence of childhood obesity also rose vividly during the last decades with more obese and overweight children growing into overweight and obese adolescents and adults. Based on WHO data, ~40 million preschool age children under 5 yr were overweight or obese in 2018. More than 340 million children and adolescents between 5 and 19 yr were classified overweight or obese in 2016. Retrospectively, child and adolescent obesity prevalence jumped from 0.7% to 5.6% in boys and 0.9% to 7.8% in girls between 1975 and 2016 (2).

1.1.1.2. REGIONAL EPIDEMIOLOGY. With the rapidly increased prevalence of obesity worldwide between 1975 and 2016 (2), remarkable regional differences were noted in obesity epidemiology (**FIGURE 1**). For example, the prevalence of obesity differs dramatically by country, ranging from 3.7% in Japan to 38.2% in the US (13). More than 50% of the global obese population lives in only 10 countries, including the United States, Brazil, China, Egypt, Germany, India, Indonesia, Mexico, Pakistan, and Russia (4). Moreover, dynamics of obesity prevalence exhibits heterogeneity across various countries in the steepness of rise, deceleration, and acceleration of obesity. Although China and India possess abundant obese populations, the prevalence of obesity in these two countries is relatively low due to the population base (~5.7% and 7.0%, respectively, in 2015) (13). America and Europe still remain the two regions with the highest prevalence of overweight and obesity in 2015 (3). In North America, the occurrence of overweight jumped from 45.3% in 1980 to 64.2% in 2015 and the frequency of obesity rose from 12.9% in 1980 to 28.3% in 2015 (3). The prevalence of obesity was 42.4%, and severe obesity approached 9.2% in the US in 2017–2018. In Europe, the prevalence of overweight changed drastically from 48% in 1980 to 59.6% in 2015 and that of obesity escalated from 14.5% in 1980 to 22.9% in 2015 (3). Along the same line, the numbers of overweight rose from 37.9% in 1980 to 49.6% in 2015 and that of obesity jumped from 11.8% in 1980 to 19.6% in 2015 in the Eastern Mediterranean region. In Africa, the rate of overweight and obesity rose from 18.5% to 34.5% and 6.2% to 12.7%, respectively, between 1980 and 2015. Although with the lowest global ranking, inclinations in overweight and obesity also hiked in the West Pacific region (China, Japan, Philippines, Vietnam, and South Korea) during the past three decades. In particular, the prevalence of overweight more than tripled from 7.8% to 29.9% in China. Likewise, the incidence of overweight escalated from 10.9% in 1980 to 24.3% in 2015, and the rate of obesity rose from 1.7% in 1980 to 6.2% in 2015, in the Southeast Asian region (3). Globally speaking, regions from south Asia, southeast Asia, the Caribbean, and southern Latin America seem to experience the most accelerated increase in BMI value (2).

1.1.2. Disease burden of obesity.

Obesity, when uncorrected, is accompanied with an increased morbidity and mortality of noncommunicable

diseases, particularly CVD, musculoskeletal disorders, and certain forms of cancers (breast, ovarian, prostate, liver, kidney, and colon cancers) (5, 6). Obesity results in the onset of a cluster of unfavorable chronic disorders, which commonly trigger profound metabolic pathologies [e.g., hypertension, hyperinsulinemia, dyslipidemia, glucose intolerance, and type 2 diabetes mellitus (T2D)] (14–18). Notably, the World Obesity Federation and the American and Canadian Medical Associations have all affirmed obesity as a chronic developing illness in addition to its role as just a risk factor for other comorbidities (19). In 2015, excess weight underwrote 4.0 million (ranging 2.7–5.3 million) mortalities and 120 million (ranging 84–158 million) disability adjusted life years (DALYs) globally (20, 21). Nearly 39% of deaths and 36% of DALYs associated with high BMI were reported in those with a BMI $\geq$30 kg/m^2. Various obesity-related chronic diseases have been noted for the economic burden in obesity. Among which, CVD accounts for more than two-thirds of mortalities linked with high BMI and 66.3 million DALYs (20). Compared with those with normal weight, individuals who gain substantial weight from young and middle age display a 22% and 49% greater risk of all-cause mortality and CVD mortality, respectively (22).

Obesity increases risks of multiple diseases and poor mental health, all of which might lead to compromised life quality, lower productivity, unemployment, and social hardships and higher healthcare costs (23). For instance, osteoarthritis, a popular aftermath of obesity, is one leading cause of disability and retirement. In the US, the healthcare expense for a single obese individual was estimated to be $1,901 annually in 2014, inferring a total cost of $149.4 billion on obesity nationally. In Europe, overweight- and obesity-induced direct and indirect cost was equivalent to 0.47–0.61% of the gross domestic product (3). According to a systematic review, medical costs of obese people were 32% more compared with lean individuals. Specially, obesity is believed to account for 31.8% of direct or healthcare costs, and 68.1% of indirect costs associated with deficit of productivity and production value (7).

1.2. Etiology of Obesity

1.2.1. Environment: diet consumption and sedentary lifestyle.

The etiology of obesity is multifactorial including genetic, environmental; and behavioral aspects. In general, obesity is usually a result from a prolonged positive energy balance, that is, increased consumption of food consumption in excess of energy expenditure (in the form of heat production) (24). An important dietary determinant of obesity is the increased consumption of sugar in the form of fructose-containing sugars, sucrose, and high-fructose corn syrup, mainly refined carbohydrates used extensively in the modern food industry (25). Evidence from epidemiological studies supports a solid tie between sugar-sweetened beverage usage and BMI (26). However, the perception of obesity is recently switching away from the simplistic notion of energy imbalance, calorie counting, and single isolated nutrients toward overall dietary patterns on the complex physiological determinants of weight regulation (27). In short-term, total calories are most relevant to weight gain regardless of the types of diets. However, in long-term weight control and cardiometabolic health, healthy food-based patterns matter given the synergistic health outcome produced by the combination of foods habitually consumed (27, 28).

Several other lifestyle factors, such as sedentary behavior, circadian alignment, and sleep quality, may interact with diet to influence metabolic risk and disease propensity. Accumulating evidence supports the notion that sedentary behavior is a strong predictor of obesity and detrimental changes in metabolic traits (29, 30). Among various sedentary behaviors, TV watching, computer games, and other electronic entertainments are considered as the main culprits as screen media exposure greatly displaces physical activities and significantly prompts risks of overweight, obesity and T2D in children and adolescent (31–33). While sedentary behaviors prompt the onset of overweight and obesity in spite of "recreational" or "seasonal" physical exercise (34), it is well conceived that lack of proper and regular physical exercise is more strongly associated with obesity prevalence compared with sedentary behaviors themselves (33, 35).

Last but not least, a theory of "fetal programming of adult disease" has evolved linking the increased prevalence of adulthood obesity and metabolic complications with intrauterine and early postnatal environmental stress (36–38). Both under- and overnutrition during intrauterine and early postnatal stages may adversely impact adulthood phenotypes and organ function especially insulin sensitivity, adiposity, myocardial morphology, and function (38–43). Moreover, epigenetic transgenerational inheritance of susceptibility to adiposity or obesity in subsequent generations has been documented with ancestral exposure (maternal or paternal) to environmental toxicants and altered nutrition (44, 45).

1.2.2. Genetics and epigenetics.

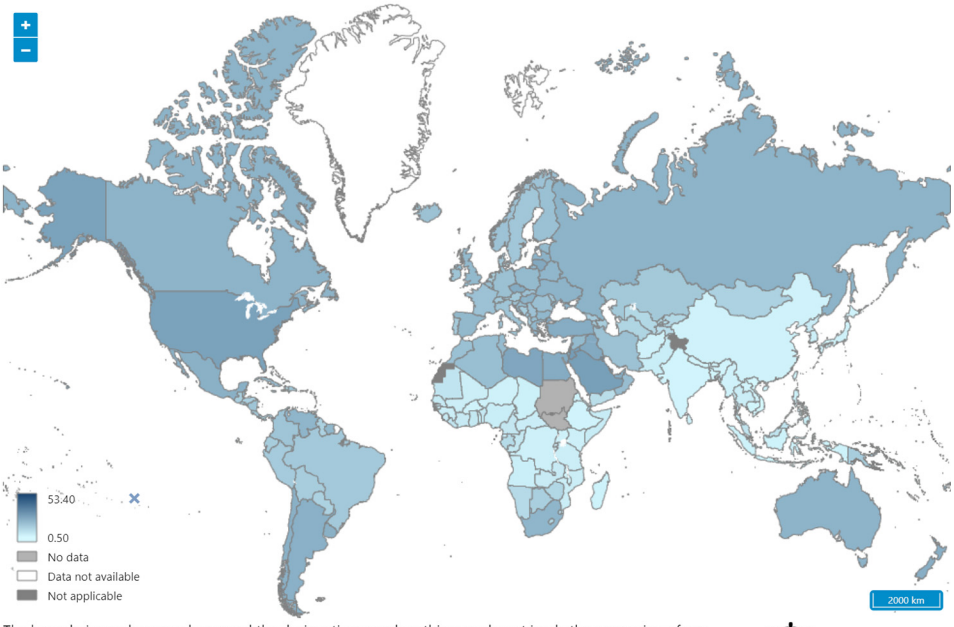
Obesity is an anthropometric trait resulting from a complex interplay of genetic and environmental factors. The gene-environment interactions are generally responsible for changes in gene expression and epigenetic

Prevalence of obesity among adults, BMI ≥ 30 (age-standardized estimate) (%)

FILTERS

Year
1996

Sex
Both sexes



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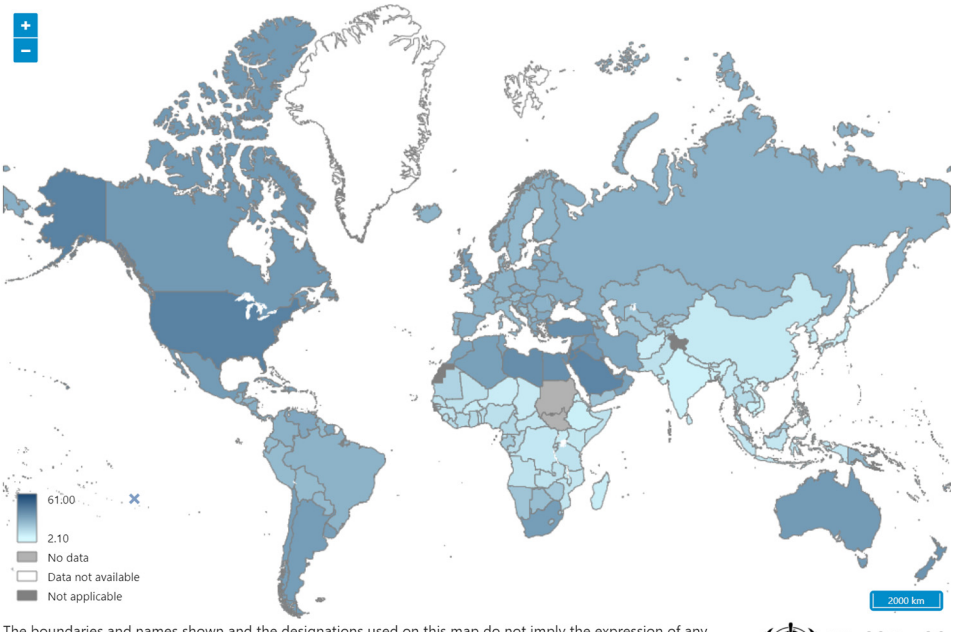
World Health Organization

Prevalence of obesity among adults, BMI ≥ 30 (age-standardized estimate) (%)

FILTERS

Year
Latest

Sex
Both sexes



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World Health Organization

modifications leading to excess body fat and obesity (46). Although parental obesity is listed as an important risk factor for childhood and/or adolescent obesity (47), obesity does not usually follow the Mendelian rule of inheritance and genetic factors only explain a small proportion of the development of obesity (1, 48). The obesity trait may be triggered by both single genes (monogenic) and multiple genes (common or multifactorial obesity). In addition to genetic factors, epigenetic contributions (i.e., modifications pre- or posttranslation) also play an essential role in obesogenesis. Loss-of-function mutations in genes including LEP, LEPR, MC4R, PCSK1, ADCY3, hypothalamic proopiomelanocortin (POMC), and SIM1 have all been associated with monogenic obesity (49). Mutations of the leptin gene, noted in rare cases of extremely obese children/mice, underscores a role for leptin-modulated energy balance through melanocortin-dependent/independent mechanisms (50, 51). Leptin normally sends signals of sufficient fuel storage from adipose tissues to the hypothalamus which promotes satiety by production of α-melanocyte-stimulating hormone (α-MSH) and its binding to the MC4 receptor (MC4R) in response to leptin stimulation. Mutations (in the forms of frame shift, missense or deletion) in POMC and MC4R have been reported in severe obesity (52–55). Indeed, mutations in MC4R are deemed the most prevalent mutations in monogenic obesity (52). Up to 5% of individuals with childhood obesity are carriers of heterozygous MC4R mutations (56, 57). Enzymes including prohormone convertase 1 (PCSK1) processes melanocortin peptides (58). Heterozygous mutations in PCSK1 were noted to alter POMC processing and promote obesity associated with glucocorticoid deficiency and hypogonadotropic hypogonadism (59).

The majority of obese subjects is representatives of "common obesity." Recently, genome-wide association study (GWAS) analysis has paved the way in the elucidation of the complex genetics underlying common obesity. Up-to-date, large-scale GWAS has identified over 800 single nucleotide polymorphisms tightly associated with BMI (60, 61). These GWAS findings revealed various loci associated with obesity related genes in energy and lipid metabolism (FTO, RPTOR, and MAP2K5) (61), insulin response [TCF7L2 and insulin receptor substrate-1 (IRS1)] (61), adipogenesis [CEBPA, PPARG, bone morphogenetic protein (BMP)-2, HOXC/miR196, SPRY1, TBX15, and PEMT] (62), and neurocircuits of appetite and satiety (BDNF, MC4R, and NEGR) (63–65). Although many more loci linked to obesity have been unveiled, merely 5% of the variance of BMI could be explained by genetic factors (60).

Obesogenesis is also regulated by epigenetic changes. Among various forms of epigenetic modifications, DNA cytosine (C) methylation (CpG) may represent the most stable and well-defined epigenetic machinery involved in obesogenesis (66, 67). Saturated fat, refined carbohydrate, and other dietary factors may all strongly affect gene-specific DNA methylation in obesity. For instance, DNA methylation of adipokines leptin and adiponectin is believed to be connected to BMI and LDL cholesterol levels (68). Furthermore, high methylation of POMC is associated with weight regain in those individuals who just achieved weight loss (69). Interestingly, compared with lean subjects, MSH-positive neurons are much more abundant in obese individuals, suggesting a regulatory role for methylation in POMC downstream signaling components (69).

1.2.3. Animal models of obesity.

Animal models of obesity are widely employed in experimental obesity research, which encompass monogenic and polygenic as well as obesogenic diet-induced models (70, 71). Murine obese models usually exhibit hyperphagia and increased energy metabolism and various comorbidities of obesity, including hyperglycemia, insulin resistance, or diabetes-like syndromes (71–74). It is noteworthy that levels of energy expenditure could be mistakenly assessed given that metabolic inactive mass [for example, the "inert" triacylglycerol (TG)] accounts for the majority of increased weight in obesity and major difference in body mass between lean and obese mice (75). Therefore, energy expenditure in murine obesity models should be calculated with special caution, for example, using the animal lean body mass for normalization. Manipulations of genes commonly involved in leptin pathway provoke obesity, including Lep^{ob}/Lep^{ob} mice or db/db mice and their rat counterparts, the Zucker or Zucker Diabetic Fatty (ZDF) rats. These rodent models present either a loss of leptin (Lep^{ob}/Lep^{ob}) or a mutation in leptin receptor (Lep^{db}/Lep^{db}), imposing severe leptin resistance. Spontaneous mutation that yields Lep^{ob}/Lep^{ob} mice presents obesity, hyperphagia, hypothermia, and increased energy expenditure capacity. Lep^{ob}/Lep^{ob} mice also develop elevated circulating glucocorticoid levels and severe insulin resistance associated with hyperglycemia and hyperinsulinemia (76). The phenotype of

FIGURE 1. Increase in obesity prevalence over the past 20 yr (1996-2016): According to the World Health Organization's (WHO) data, 39% of adults aged 18 yr and over (39% of men and 40% of women) were overweight in 2016 worldwide. Overall, about 13% of the world's adult population (11% of men and 15% of women) were obese in 2016. Reproduced from WHO's Global Health Observatory (GHO) Data (9) with permission. BMI, body mass index.

Lep^{db}/Lep^{db} obese mice is reminiscent of that seen in Lep^{ob}/Lep^{ob} mice (insulin resistance, diabetes mellitus, and hyperglycemia), with marked early onset obesity, albeit with hyperleptinemia in comparison with the Lep^{ob}/Lep^{ob} mice (71, 77–80). Likewise, obese Zucker (fa/fa or "fatty" rat) and Koletsky rats are leptin receptor deficient. Koletsky rats are characterized by null mutation of leptin receptor, with essentially undetectable leptin receptor mRNA levels, whereas Zucker fatty rats are featured by a genetic processing mistake in leptin receptor (fa/fa mutation), leading to intracellular trapping of the receptor. These murine models of obesity exhibit hyperphagia, increased energy expenditure, compromised glucose tolerance, and growth deficits courtesy of hypothyroidism and low circulating levels of growth hormone (70, 80–83). Despite the fact that monogenic models are practical in the study of specific mechanistic aspects of obesity, they usually cannot truly recapitulate human obesity. Polygenic obesity models are thus more comparable with the polygenic nature of human obesity. Diet-induced rodent obesity models are commonly employed with exposure to high-fat or high-energy diets, prompting an obese phenotype with the extent of weight gain depending on nature and duration of dietary intake. Diet-induced obese rodents usually develop leptin resistance, insulin resistance, and hypertriglyceridemia before the onset of full-blown obesity (71, 84–91). In addition, lesions in specific brain regions, including ventromedial hypothalamus (92) and hypothalamic paraventricular nucleus (93), also result in overt obese phenotype in rodents.

1.3. Obesity and Cardiovascular Disease

1.3.1. Obesity and overall CVD prevalence.

Ample evidence from both clinical and experimental settings supports the role for obesity in the pathogenesis of CVD, including heart failure (HF) (72, 87, 89, 94–106). Not only is obesity closely intertwined with greater prevalence of coexisting risk factors for CVD such as coronary artery disease, hypertension, diabetes mellitus, and obstructive sleep apnea (2, 3), but obesity alone also impacts myocardial structure and pump performance (manifestations of obesity cardiomyopathy) (107). More recently, a new term "cardiometabolic-based chronic disease" (CMBCD) was introduced to boost timely and continued preventive care for cardiometabolic diseases rooted from genetics, environment, and behavior cues. Reported endpoints for CMBCD encompass coronary heart disease, heart failure, and atrial fibrillation (AF), all of which are commonly present in obesity (108). Early evidence for obesity-related CVD includes findings from the Framingham Heart Study that demonstrated an elevated risk of coronary disease, stroke, heart failure, and CVD death in obesity independent of other common risk factors, such as age, gender, smoking, cholesterol, blood pressure, and glucose intolerance (109). Population-based findings also reveal a tight correlation between increased BMI and earlier CVD morbidity (110, 111) or cardiometabolic multimorbidity (112). Moreover, overweight in adolescence is associated with increased CV abnormalities, especially dilated cardiomyopathy (113), and higher all-cause mortality in adulthood (114). Cardiomyopathy, manifested as left ventricular (LV) enlargement and subclinical cardiac dysfunction in the absence of coronary artery disease, is a common cause of HF (107, 115). For instance, elevated BMI in women of childbearing age results in increased risk of cardiomyopathy, particularly dilated and hypertrophic cardiomyopathies (116) (**FIGURE 2**). With the increasing evidence depicting changes in cardiac structure and function in mildly to moderately obese individuals, it is becoming evident that obesity serves as an independent risk factor for heart failure. This scenario may be expanded to embrace myocardial anomalies in obese subjects that cannot be credited to coronary artery disease, hypertension, diabetes mellitus, or any other confounding etiologies. However, the correlation between BMI and cardiac function gets more complicated with the appearance of "obesity paradox" (117, 118), whereby high BMI appears to confer neutral or even beneficial effects in subgroups who fit into "metabolically healthy obese" category. Better understanding of the mechanisms underlying obesity-related CVD, especially obesity cardiomyopathy, should help to guide clinical decisions according to the comprehensive assessment of obesity. Here we will summarize characteristics of cardiac remodeling, emerging mechanisms, and therapeutic approaches targeting cardiomyopathy in the setting of obesity, with particular emphasis on advances in cardiac metabolic alternations and subcellular abnormalities involved in the development of obesity cardiomyopathy (**FIGURE 3**).

1.3.2. Impact of obesity on coronavirus disease 2019-associated cardiovascular outcome.

Coronavirus disease 2019 (COVID-19), a pandemic respiratory illness caused by a novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (119), was first detected in late 2019 in Wuhan, China and then spread rapidly across the world. Recent evidence has indicated a close tie between obesity and severity of COVID-19 (120). Clinical data noted an increased risk of COVID-19 severity and mortality in obese patients. In a meta-analysis involving 7,196 patients from 13 independent studies, obesity was associated with an increased risk of critical

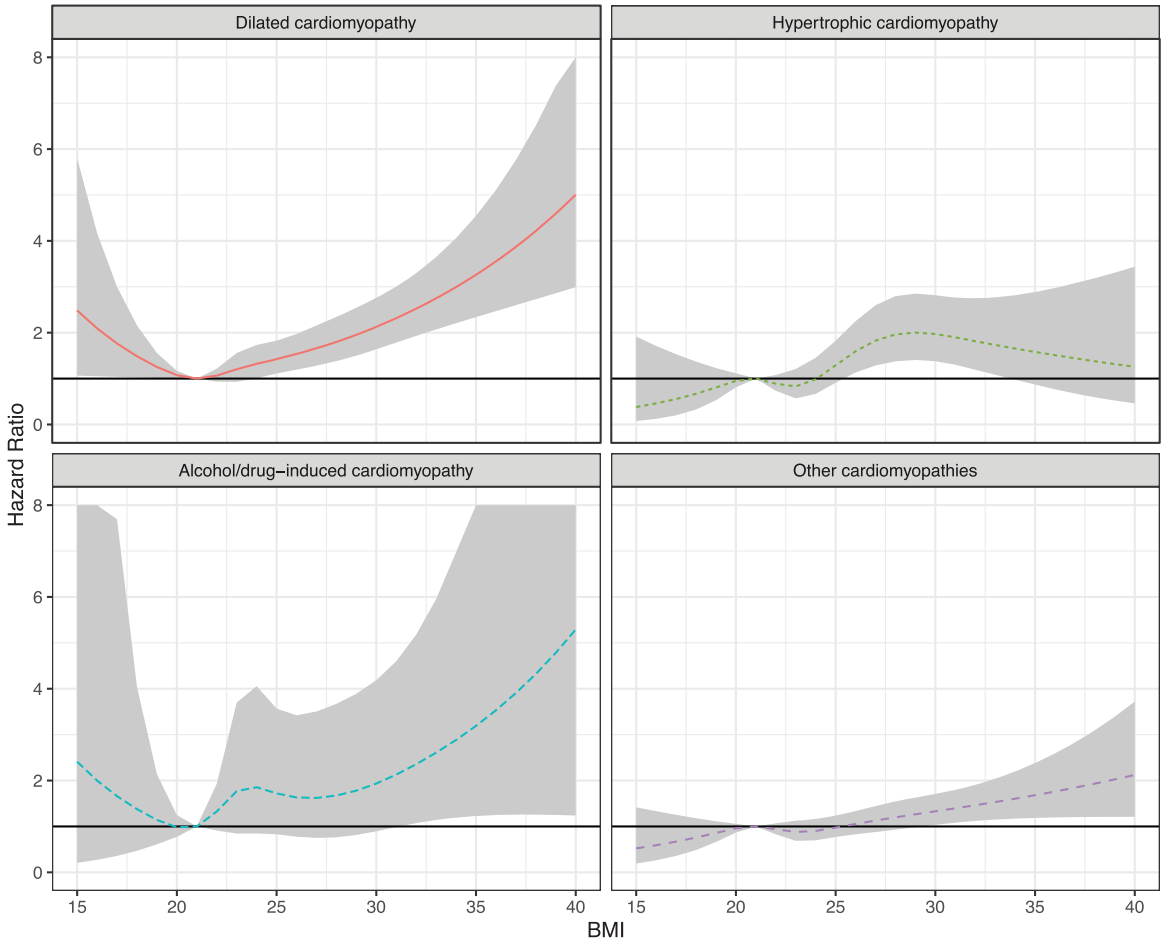
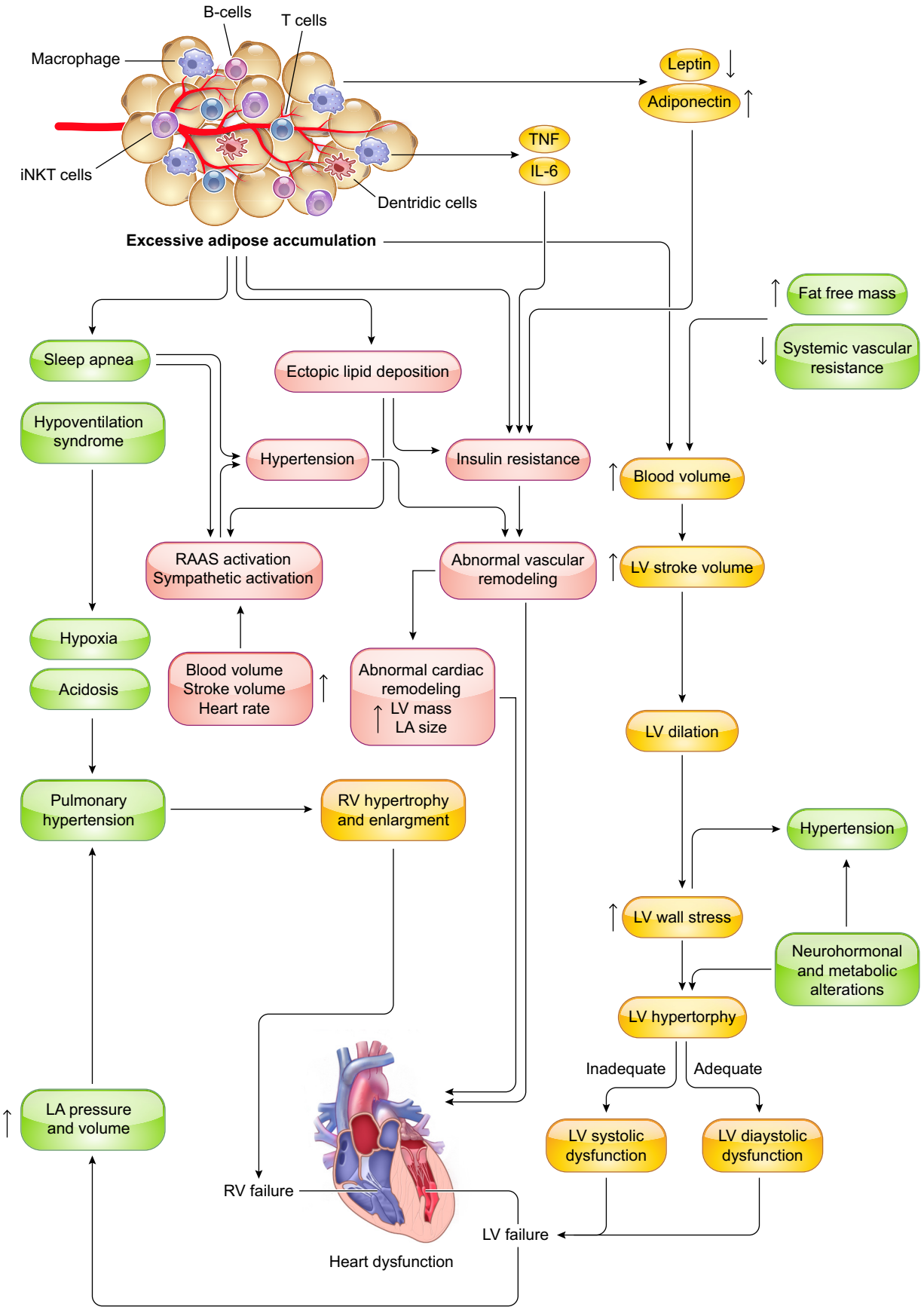


FIGURE 2. Association between body mass index (BMI) in young women and risk for cardiomyopathies: The model is adjusted for age, year, parity, comorbidities at baseline, smoking, and level of education (n = 1,339,527). Reproduced from Robertson et al. (116) with permission.

illness in hospitalized COVID-19 patients (121). In 383 patients with COVID-19, overweight was linked to a 1.84-fold odds, while obesity displayed a 3.40-fold odds of developing severe COVID-19 in comparison with patients with normal weight (122). In another independent study involving 5,279 patients with COVID-19 in the New York City, BMI >40 kg/m^2 was the second strongest independent predictor of COVID-19 hospitalization, only after old age (123). Along the same line, the prevalence of obesity was 1.89 times higher in severe COVID-19 patients than the general French population (124). Ample clinical evidence has depicted that CVD and diabetes mellitus are the leading causes of a more severe course of COVID-19 (125). Given the propensity of obesity to prompt CVD including heart failure, hypertension, coronary heart disease, stroke, AF, renal disease, and diabetes mellitus (126–128), being obese itself with high ectopic fat is deemed a unifying risk factor for severe SARS-CoV-2 infection, inflammation, poorly coordinated innate and adaptive responses, inadequate antibody response, cytokine storm, and compromised cardiorespiratory reserve (120, 129). Even in the absence of comorbidities of obesity, the presence of hypertension and metabolic disorders in obesity might result in increased susceptibility to infection via thrombotic events, atherosclerosis, cardiac dysfunction, and impaired immunity (130). Overweight or obese patients exhibit poor endothelial function, cardiorenal and respiratory diseases, which may all negatively impact COVID-19 outcomes (131). On the other side of the coin, reduced physical activity, unhealthy dietary habit, stress, and fear during the COVID-19 pandemic may escalate weight gain and obesity (120). From the molecular biology perspective, SARS-CoV-2 binds to the angiotensin-converting enzyme 2 (ACE2) receptors in the lung and other organs. With overactivated renin-angiotensin-aldosterone system (RAAS) in obesity, the abundant presence of ACE2 in obesity should ease the entrance of SARS-CoV-2 into adipocytes, making adipose tissues an unexpected viral reservoir before the spread of virus to other organs (131). In this context, overweight or obesity should be considered as an


B-cells
T cells
Macrophage
iNKT cells
Dentridic cells
Leptin
Adiponectin
TNF
IL-6
Excessive adipose accumulation
Fat free mass
Systemic vascular resistance
Sleep apnea
Ectopic lipid deposition
Hypoventilation syndrome
Hypertension
Insulin resistance
Blood volume
RAAS activation
Sympathetic activation
Abnormal vascular remodeling
LV stroke volume
Hypoxia
Acidosis
Blood volume
Stroke volume
Heart rate
Abnormal cardiac remodeling
LV mass
LA size
LV dilation
Pulmonary hypertension
RV hypertrophy and enlargment
Hypertension
LV wall stress
Neurohormonal and metabolic alterations
LV hypertorphy
Inadequate
Adequate
LA pressure and volume
LV systolic dysfunction
LV diaystolic dysfunction
RV failure
LV failure
Heart dysfunction

independent risk factor for COVID-19 although more scrutiny is warranted to evaluate the clinical management of COVID-19 and associated cardiovascular complications in obesity.

2. CARDIAC REMODELING IN OBESITY

The nomenclature "obesity cardiomyopathy" refers to cardiac morphological, functional, and metabolic abnormalities originating from obesity alone (94, 95). In some cases, the term "metabolic cardiomyopathy" may be used in reference to the broad setting of metabolic disorders including insulin resistance, diabetes mellitus, and obesity (132, 133). In general, long-term obesity is closely associated with cardiac remodeling, characterized as LV hypertrophy, cardiac fibrosis, and diastolic dysfunction that eventually evolves to overt heart failure (**FIGURE 3**). Fat accumulation, especially disproportionate deposition of metabolically active visceral adipose tissue (VAT) and pericardial fat, drives a higher cardiac output (CO) and workload, and subsequently an enlargement of the LV to meet increased energy requirements (134). Obesity is accompanied by alternations in nutrition, gut microbiota, and neurohumoral activity that compromise cardiac energy metabolism, contractile and relaxation function, and cardiac survival (135, 136) Meanwhile, changes in nutrition status, gut microbiota, and physical exercise are also indispensable for the development of CVD in obesity (137–139). In the absence of lifestyle intervention and targeted drug treatment, obesity impairs cardiac structure and function. It is noteworthy that the cardiac pathological phenotype of obesity varies and can be manifested as either HF with preserved ejection fraction (HFpEF) or reduced ejection fraction (140, 141). In addition to morphological changes, obesity impacts myocardial electrophysiology, resulting in an increased prevalence of AF (142). Obesity-related hemodynamic changes, maladaptive myocardial structural remodeling, and cardiac dysfunction will be briefly summarized (**TABLE 1**). Regardless of structural or electrophysiological remodeling abnormalities, obesity serves as an independent culprit factor for the occurrence of cardiac hypertrophy and contractile dysfunction (17, 158, 159).

Although limited data are available, sex difference exists for obesity-associated CVD outcome including a higher mortality risk with increased abdominal fat in female but not male heart failure patients (160). Despite that heart failure and various cardiomyopathies are generally less frequent in women, cardiomyopathies rooted from metabolic derangement seem to be more popular in women than men (161, 162).

Furthermore, most obese individuals suffer from at least one of the comorbidities such as hypertension, sleep apnea, or diabetes mellitus (163, 164). The concurrent presence of coronary heart diseases, hypertension, and the unique obesity cardiomyopathy seems to independently and cooperatively determine anatomic and functional myocardial pathologies in patients with obesity and other comorbidities such as heart failure. Simply launching a defined relationship between obesity and cardiomyopathy is challenging and complicated, since obesity is often present for years before manifestation of any cardiac pathological phenotype. Limited longitudinal data have been accumulated for chronological alterations in cardiac structure and function in obese but otherwise healthy individuals, making it difficult to determine the precise onset timing of "obesity cardiomyopathy" (165).

2.1. Hemodynamics

Although a paradoxical benefit exists in overweight and class I obesity (118, 126, 140, 166–174), it is well documented that obesity produces hemodynamic alterations that generally predispose to unfavorable changes in ventricular structure and function, contributing to the etiology of obesity cardiomyopathy (175) (as summarized in **FIGURE 3**).

2.1.1. Increased blood volume.

Obese patients have an increased total and central blood volume (140, 176, 177). The increase of blood volume is predominantly the result of elevated renal sodium retention and higher metabolic requirements. The etiology of expanded blood volume and hypertension in obesity, in particular visceral adiposity, involves several pathophysiological processes including activation of sympathetic nervous system and renin-angiotensin-aldosterone system (RAAS), hyperinsulinemia, and natriuretic peptide downregulation, all of which could impair renal capacity to excrete Na, leading to Na retention.

FIGURE 3. Overall impact of excessive adipose accumulation on cardiac hemodynamic and ventricular function: Under severe obese condition, alterations in ventricular function and abnormalities in cardiac hemodynamic lead to heart failure. Severe obesity induces left ventricular (LV) hypertrophy, which may be eccentric (predominant in normotensive severe obesity) or concentric (predominant in severe obesity and obesity with established systemic hypertension). It is uncertain to what extent metabolic alterations including leptin/insulin resistance, lipid toxicity, and altered renin-angiotensin-aldosterone system (RAAS) may lead to obesity cardiomyopathy. RV, right ventricular; LV, left ventricular; TNF, tumor necrosis factor; IL-6, interleukin-6; iNKT cells, invariant natural killer T cells; LA, left atria.

Table 1. ***Summary of evidence for cardiomyopathy in obese individuals***

Authors (Year) (Ref. No.)	Patient Information	Presentation of Heart Dysfunction in Obesity
Dhuper et al. (2011) (143)	213 obese (BMI = 36.53 ± 0.53) vs. 130 lean subjects	Higher LV mass index, wall thickness, LA index, more aberrant diastolic function by tissue Doppler E/Ea septal, E/Ea lateral, myocardial performance index, Doppler mitral EA ratio, and similar systolic function
Shah et al. (2011) (144)	223 obese and 157 obese diabetic subjects vs. 232 lean subjects	Abnormal cardiac geometry, increased systolic function, and decreased diastolic function
Utz et al. (2011) (145)	65 overweight/obese but otherwise healthy women	Higher myocardial triglyceride levels, reduced left ventricular diastolic, but not systolic function, and increased remodeling index in women with insulin resistance compared with insulin-sensitive women
Canepa et al. (2013) (146)	88 obese vs. 154 nonobese patients	Increased LV mass index, LV posterior wall thickness but not septal wall with increased hypertension; higher LV stroke volume; no changes in LV systolic and diastolic function
Olivotto et al. (2013) (147)	275 adult HCM patients	Increased LV mass and higher risks for developing New York Heart Association (NYHA) functional class III to IV symptoms in obese patients
Dahiya et al. (2015) (148)	35 obese vs. 34 nonobese patients	Lower peak myocardial relaxation velocity, greater filling pressures; Higher LV mass index, left atrial volume index, and LV interventricular septal thickness
Rider et al. (2015) (149)	59 obese vs. 40 normal weight subjects without identifiable CV risk factors	No changes in systolic function; Impaired peak radial and longitudinal diastolic myocardial velocity, prolonged time-to-peak longitudinal diastolic velocity; lower peak longitudinal diastolic strain and time-to-peak longitudinal diastolic strain rate
Yagmur et al. (2017) (150)	40 obese vs. 40 normal weight subjects	No changes in LV diameters and EF; Impaired LV diastolic function (higher transmitral deceleration time, isovolumetric relaxation time, and peak late diastolic tissue Doppler velocity values); Impaired LA reservoir and pump functions
Finocchiaro et al. (2018) (151)	1,033 sudden cardiac death patients (≤35 yr): 212 obese vs. 821 lean subjects	Increased prevalence of left ventricular hypertrophy (12% vs. 2%) and coronary artery disease (12% vs. 3%); less sudden arrhythmic death syndrome (50% vs. 60%)
Blomstrand et al. (2018) (152)	384 patients with T2D, and 184 nondiabetic subjects	Lower LVEF and global longitudinal strain values and increased E/e' (the ratio between early diastolic mitral flow and annular motion velocities) in obese subjects with or without T2D
El Saiedi et al. (2018) (153)	42 obese vs. 30 healthy children	Higher ratio of transmitral early diastolic filling velocity to septal peak early diastolic myocardial velocity (E/e') without LVH
Balaji et al. (2019) (154)	504 children with HCM: 140 obese vs. 364 nonobese patients	Increased posterior wall thickness (PWT) but not interventricular septal thickness (IVST)
Fumagalli et al. (2019) (155)	3282 HCM patients: 1,280 preobese and 1,040 obese vs. 962 normal weight subjects	Increased likelihood of NYHA class of III/IV [preobesity, 138 (10.8%); obesity, 215 (20.7%); normal weight, 87 (9.0%)], heart failure (preobesity vs normal weight: HR, 1.192; 95% CI, 0.930–1.1530; obesity vs normal weight: HR, 1.885; 95% CI, 1.485–2.393) and AF
Park et al. (2019) (156)	28,679,891 individuals	Increased incidence of clinical HCM after multivariate adjustment, with a hazard ratio per 1 kg/m^2 increase in BMI of 1.063 (95% confidence interval 1.051–1.075)
Robertson et al. (2020) (116)	1,388,571 women (18-45 yr)	Increased risk for cardiomyopathy, particularly for DCM (HR = 4.71 for BMI ≥35 kg/m^2 vs. BMI 20-22.5 kg/m^2)
Litwin et al. (2020) (157)	11-year follow-up of 254 subjects	Increased BMI was related to increases in LV end-diastolic volume, LV mass, and left atrial volume and decreases in early/late mitral diastolic flow velocity ratio and E-wave deceleration time

E/Ea, early transmitral flow velocity to early diastolic velocity of the mitral annulus; EA, early to late transmitral flow velocity; HCM, hypertrophic cardiomyopathy; DCM, dilated cardiomyopathy; LVH, left ventricular hypertrophy; BMI, body mass index; CI, confidence interval; HR, heart rate; AF, atrial fibrillation; T2D, type 2 diabetes.

Furthermore, overweight/obese individuals generally exhibit a higher level of salt intake, contributing to elevated blood pressure (BP) and blood volume. Obese individuals are also prone to increased salt sensitivity with higher BP hikes with a given amount of salt intake, while genetic variants in salt sensitivity would also affect obesity propensity (178–180).

Obesity commonly causes hypoxemia without concurrent cardiopulmonary anomalies through increased oxygen consumption and decreased lung volumes with normal breathing (181). Along with increased metabolic requirements, increased occurrence of the sleep apnea/hypoventilation syndrome further aggravates hypoxemia in obesity. Hypoxemia promotes erythropoietic activity, as indicated by elevated plasma levels of erythropoietin, the transferrin receptor, and hemoglobin, all of which result in further blood volume elevation (182).

2.1.2. Increased CO.

Similar to arteriovenous shunts in severe liver disease, overweight/obesity, especially abdominal adiposity, is associated with an increased risk of high-output HF (111, 183–186), possibly due to higher filling pressure and increased CO (187, 188). With increased blood volume and stroke volume (SV), CO is generally elevated in overweight/obese subjects with little change in heart rate (189). It should be mentioned that although CO remains relatively high in hypertensive obese patients, it is still lower than that in normotensive obese individuals probably due to increased systemic vascular resistance in hypertension (190).

Abnormal indexes of stroke volume (SV) and CO may be obscured by obesity. Normalization of SV and CO for ideal body surface area (BSA) or height to its age-specific allometric power should provide a more accurate and better estimate for the impact of obesity on LV systolic function (190). Interestingly, fat-free body mass (FFM) is more strongly correlated with SV and CO compared with fat mass and other adiposity variables (191).

Central fat distribution (CFD) is closely correlated with severe abnormalities in body composition and higher CO, independently of FFM/fat mass (FM) in overweight individuals (192). Nonetheless, recent data also suggest that CO may be lower along with higher systemic vascular resistance in central obesity compared with those with peripheral obesity (193, 194).

2.1.3. Increased blood pressure.

Overweight/obesity is a predominant risk factor for the etiology of hypertension (195, 196), although the precise mechanisms coupling hypertension to obesity remain elusive. As aforementioned, Na retention, altered salt sensitivity, overflow of sympathetic nervous system, and activation of RAAS and aldosterone/mineralocorticoid receptor (MR) systems as well as physical compression of kidneys by visceral fat pad may all play an important role in the impaired renal-pressure natriuresis (197, 198). Further evidence has noted impaired tubule-glomerular feedback and renal retention of Na in obese subjects. Elevated BP, dyslipidemia, and hyperglycemia, the three most predominant risk factors for obesity, may be responsible for at least 45%-50% of CVD incidence, particularly coronary heart diseases in obese individuals (14). This is strongly supported by the favorable cardiovascular outcomes in obesity resulting from reductions in BP [telmisartan (199)], glucose [sodium/glucose cotransporter 1 (SGLT1) inhibitor (200)], and lipid [orlistat (201)].

2.1.3.1. ARTERIAL STIFFNESS. Arterial stiffness, a devastating pathological process featured by progressively loss of distensibility of large arteries, emerges as an independent risk factor exacerbating the development of CVD in obesity. Excess caloric intake prompts the onset and development of vascular stiffness to compromise vascular function via endothelial dysfunction, extracellular matrix remodeling, calcification, and inflammation (202–204). Arterial stiffness is usually monitored clinically using pulse wave velocity (205, 206). Weight gain and metabolic disorders occur before, or concomitant with, arterial stiffening (189, 207–212). This reduction of cushioning capacity imposes multiple consequences on cardiovascular health, including elevated systolic blood pressure, incident hypertension, increased penetration of pulsatile energy into microvasculature of target organs, and a rise in coronary perfusion pressure and myocardial wall stress, all of which prompt LV remodeling, dysfunction, and heart failure (202, 203, 211, 213, 214). Thus arterial stiffness may be evaluated through comprehensive assessment of arterial distensibility in the clinical setting to pinpoint vascular health and predict future cardiovascular risk. Many, although not all, studies have found that weight loss reduces arterial stiffness, indicating the reversible nature of obesity-induced vascular stiffness (212, 215, 216). A better understanding of arterial stiffness in overweight and obesity should assist therapeutic strategies to reduce obesity-associated inordinate CVD risks.

2.1.3.2. PERIPHERAL RESISTANCE. Hypertension is evoked by increased CO and/or increased peripheral vascular resistance (PVR) (217). Normotensive obese patients commonly display low PVRs (175, 218). Total PVR generally correlates inversely with BMI while it is positively correlated with waist/hip ratio in stress conditions, indicating a much more determining role for

central obesity (as opposed to BMI) in the genesis of elevated PVR (219).

2.1.3.3. BLOOD PRESSURE. Overweight/obesity possesses a close relationship with high BP (195, 220, 221). Resistant hypertension is more prevalent with obesity (222). Compared with lean subjects, obese subjects often exhibit a higher incidence of nondipping hypertension, based on a 24-h BP obtained using an ambulatory blood pressure monitor (223, 224). Patients displaying a nondipping pattern suffer from more hypertension-induced organ damage such as LV hypertrophy, microalbuminuria, and stroke, leading to poor overall cardiovascular outcomes (224). Interestingly, overweight and obesity tend to exhibit lower central systolic blood pressure as compared with lean patients, especially in women (225).

In hypertensive patients receiving antihypertensive therapy, a higher BMI value is typically linked with much smaller BP reduction-associated benefit in LV remodeling and LV systolic function (226), which contributes to higher CVD mortality in obese hypertensive. Weight loss using antiobesity medications such as orlistat is associated with an overt BP drop in overweight/obese subjects (227). Furthermore, bariatric surgery may also serve as a useful alternative strategy for BP control in obese hypertensive patients (228).

A sexual dimorphism was noted in the hemodynamics pattern in middle-aged overweight or obese hypertensive individuals, in particular with respect to total PVR (195). Although the sex-specific intrinsic BP regulatory mechanisms are absent in nonobese subjects, multiple sex differences exist in terms of regulation of BP and hemodynamics in overweight/obese individuals at the molecular, cellular, and tissue levels. In particular, a number of governing machineries involved in the development of hypertension and CVD, including the sympathetic nervous system, the RAAS, and the immune system, display a sexual dimorphism (229). Moreover, age also plays a key role as nonobese premenopausal women exhibit a much higher degree of cardioprotection than age-matched men (although such benefits diminished with onset of menopause) (229). Furthermore, both sex chromosome complements and sex hormones such as estrogen and testosterone likely participate in gender-related differences in BP and CVD. The advantage in female longevity may limit cell senescence signaling and hypertensive organ damage in nonobese women. Last but not least, certain sex-related difference in lifestyle, such as smoking, drinking, and dietary intake, may also influence BP and CVD between men and women (230). Importantly, female advantage in cardioprotection disappears with obesity, reminiscent to that seen in diabetes mellitus (231–235).

2.1.4. Increased LV wall stress.

One of the main obesity-associated changes in hemodynamics is the rising LV wall stress and tension. In normotensive obesity, elevated central blood volume, stroke volume, and CO are the main driving forces for LV wall stress, which predisposes LV dilatation, and eccentric hypertrophy (**FIGURE 3**). Eccentric LV hypertrophy (discussed in much more detail in sect. 2.2) is likely a compensatory machinery for elevated LV wall stress and contributes to diastolic dysfunction in obesity. Systolic dysfunction may occur latter as a result of excessive wall stress if LV wall thickening fails to keep pace with chamber dilatation (236). In response to elevated tension development during systole, myocardial fibers thicken (LV hypertrophy) to maintain systolic stress at a normal range. To the contrary, elevation in resting or diastolic wall stress or tension gradually lengthens myocardial fiber, which should improve the work efficiency of ventricular chambers although it may not normalize or compensate diastolic wall stress in obese individuals (237).

2.1.5. Pulmonary hemodynamics.

Uncorrected obesity is a common comorbidity for pulmonary hypertension (PH) and influences the severity of pulmonary arterial hypertension (PAH), commonly acknowledged as primary pulmonary hypertension. A close relationship between obesity and PH is has been shown by echocardiography-based and invasive hemodynamic measurements (127). Apart from epidemiological evidence, several groups have revealed a link between obesity-related metabolic defects and pulmonary vascular remodeling utilizing various genetic and diet-induced models (238, 239). The precise pathogenic cue for obesity-induced PH is complex and undefined. Obesity exerts pathologic impact on systemic circulation through external environment of pulmonary vascular cells. With the increasingly recognized role for perivascular adipose tissue (PVAT) in CVD, adipocyte defect in obesity leads to abrupted release of endocrine and paracrine adipokines (240). Leptin and adiponectin denote two most prevalent adipokines in the pathogenesis of PH in overweight/obese subjects involving endothelial dysfunction (241, 242). Leptin-deficient (ob/ob) mice spontaneously develop PAH and pulmonary vascular remodeling (238). In addition, estrogen and its metabolites are deemed risk factors for the etiology of PAH as the effects of leptin deletion are attenuated by inhibition of endogenous estrogen production (238). It is perceived that obesity-evoked systemic and local inflammatory responses, such as inflammation, oxidative stress, PVAT expansion, and insulin resistance, all contribute to irreversible maladaptive pulmonary

vasculature remodeling, thus fostering the onset and progression of PH (243).

A number of secondary factors may also contribute to the etiology of PH in obese individuals including increased LV filling pressure and pulmonary capillary wedge pressure (PCWP) associated with LV failure (244). In fact, elevated pulmonary BP due to left heart disease is perhaps the most common type of PH. Increased LV filling pressure greatly jacks up pulmonary venous pressure and PCWP, resulting in elevated pulmonary artery pressure and right ventricular (RV) end-diastolic and right atrial pressures, the process of which is aggravated by pathological stress such as sleep apnea and obesity hypoventilation (238). Furthermore, hypoxic vasoconstriction and subsequent pulmonary arteriolar remodeling as a result of repetitive nocturnal hypoxemia may prompt right-ventricular hypertrophy and PH (245, 246). Moreover, obesity-associated chronic hyperuricemia, an independent risk factor for PH, reduces local flow within pulmonary vessels, possibly related to lowered nitric oxide production and elevated endothelin, resulting in endothelial dysfunction and ultimately rises in pulmonary artery pressures (247, 248).

2.2. Structural Changes in Obesity

2.2.1. Measurements.

2.2.1.1. ECHOCARDIOGRAPHY. Obesity leads to unfavorable changes in cardiac structure and function. With the use of echocardiography, magnetic resonance imaging (MRI), and radionucleotide, derangement in LV structure and function is noted in obesity, such as concentric remodeling and compromised diastolic and systolic function (249, 250). Moreover, left atrial (LA) enlargement is frequently noted in obesity as well (251). Two-dimensional echocardiography and tissue doppler imaging are employed to assess LV structure, myocardial systolic and diastolic function. This approach revealed much higher LV structure such as posterior and septal wall thickness, LV mass (LVM), the LVM/height and the relative wall thickness (RWT), in obese (including young, otherwise-healthy women) than nonobese individuals (252). However, LVM index (g/m^2) remained essentially unchanged in obesity.

2.2.1.2. MAGNETIC RESONANCE IMAGING. With the use of cardiac MRI, a modality, which offers significant advantages over two-dimensional (2-D) echocardiography in estimating LV mass and volume, LV mass and end-diastolic volume are shown to be positively associated with obesity severity in men and women (253). Although MRI seems to offer a more accurate and reliable measurement of LVM (254), echocardiography is still more frequently employed in the clinics due to its noninvasive nature and moderate cost

2.2.1.3. POSITRON EMISSION TOMOGRAPHY. Cardiac rubidium 82 (Rb-82) positron emission tomography (PET) has been employed for evaluation of myocardial perfusion imaging in the clinical setting courtesy of its diagnostic accuracy and low risk of radiation exposure. In obese individuals who are usually prone to soft tissue attenuation artifact with poor acoustic echocardiogram ranges, cardiac PET perfusion imaging offers a high prognostic value irrespective of BMI (255).

2.2.2. LV remodeling.

LV remodeling refers to changes in the size, shape, or structure of LV chamber and occurs more frequently in obesity (256). The Bogalusa heart study revealed an underlying role for obesity in LV hypertrophy and remodeling (257, 258). Indeed, ample evidence has suggested a positive correlation between BMI and LV mass (259) (**TABLE 1**). Obese subjects usually possess a high risk of LV hypertrophy (LVH) defined by increased ventricular mass. The prevalence of LV hypertrophy in obese normotensive subjects was ~14%, much higher than lean counterparts (5%) (260). The occurrence rate of LV hypertrophy can be up to 78% in morbid obese individuals (261), including adverse changes in LV mass, volume, geometry, and composition, ultimately resulting in impaired LV function and cardiomyopathy (256). Severe obesity and hypertension frequently coexist and impose an additive impact on LV hypertrophy (94, 262).

2.2.2.1. CHANGES IN LV MASS AND VOLUME. LV remodeling is characterized by overt changes in cardiac chamber diameter, wall thickness, volume, mass, and LV ejection fraction (EF) using imaging techniques (263). Multiple factors may promote rises in LV mass in obese individuals, with a clear positive relationship between LV mass (LVM) and seriousness of obesity. LV diastolic chamber size (diameter or volume) is also used to evaluate cardiac remodeling in obese subjects (256). LV end-diastolic volume (LVEDV) indexed to BSA is commonly employed to measure LV volume. LVEDV has been related to BSA to a power of 1.5 (264).

Physiological LV remodeling, such as exercise-induced elevation in LV end diastolic dimension (LVEDD) and LV mass, normally reverses with the cessation of physiological stimuli (e.g., exercise training). However, obesity-induced pathological remodeling seems to progress continuously and irreversibly, denoting an adverse clinical prognosis. In routine practice and clinical studies, LVM was calculated from LVEDD and interventricular septum and posterior wall thickness using echocardiography and

cardiac magnetic resonance, according to the Devereux's formula.

Although ventricular weight is typically normalized to body weight in experimental research, overweight subjects have lower ventricular mass/body weight ratio, yielding an artificial difference as a result of the increased denominator in obesity (265). Recent observations showed that patients with obesity displayed a higher LV mass when appropriately indexed to height$^{2.7}$(266). LV mass indexed to height$^{2.7}$ is more appropriately employed to avoid misleading predictions of CVD risk in obesity. Classical assessment or indexation of LV mass may underestimate or overestimate the degree of hypertrophy in obese adults. Bioelectric impedance analysis (BIA) is used to yield more precise measurements of overweight and obesity than BMI. The Strong Heart Study (SHS) has demonstrated that fat-free body mass (FFM), calculated using BIA, is the main variable determining levels of LV mass in obesity, instead of adipose mass, the waist/hip ratio, height, or height$^{2.7}$ (267). Changes in LVM display a much tighter association with FFM, suggesting the utility of FFM as a more refined parameter for normalization of LV mass (268).

2.2.2.2. FOUR-TIERED CLASSIFICATION OF LV GEOMETRY. LV hypertrophy (LVH) in obesity is typically categorized into concentric or eccentric based on RWT measured by echocardiography. However, in the traditional classification, eccentric LVH was considered a lower risk profile compared with concentric LVH, mostly as a result of indeterminate hypertrophy (269, 270). Tantiore, based on whether or not LV concentricity (measured by LV mass/LVEDV$^{0.67}$) and LVEDV are increased, cardiac magnetic resonance is used to refine the classification of LVH into a four geometric patterns as *1*) "thick hypertrophy" (increased concentricity without increased EDV); *2*) "dilated hypertrophy" (increased EDV without increased concentricity); *3*) "thick and dilated hypertrophy" (increased concentricity with increased EDV); and *4*) "indeterminate hypertrophy" (increased LVM with neither increased concentricity nor EDV) (271).

Previous research has shown the presence of concentric LV remodeling associated with decreased systolic and diastolic function in young otherwise-healthy obese women (249). A recent follow-up study included 1,699 cases of obesity cardiomyopathy with an incidence of 5.9 per 100,000 observation years. Among these, 481 were classified dilated cardiomyopathy, 246 cases were hypertrophic cardiomyopathy, 61 individuals met the criteria of alcohol/drug-induced cardiomyopathy, and 509 exhibited other forms of cardiomyopathies. Increased BMI significantly escalated the risk of these types of cardiomyopathies especially dilated cardiomyopathy, with a fivefold increase in the risk of cardiomyopathy in those with severe obesity (116) (**FIGURE 2**).

2.2.2.3. OTHER FACTORS. Obstructive sleep apnea (OSA) also serves as an independent factor of high LV mass index and abnormal LV geometry in obesity, likely due to increased blood pressure, heart rate, intermittent hypoxia, sympathetic tone, and negative intrathoracic pressure during airway obstruction (272). It seems that degree of sustained hypoxemia, rather than the number of apneic and hypopneic episodes, contributes to the development of LV hypertrophy (261, 273). Obese individuals with OSA displayed increased left atrial volume index, which predisposes them to atrial fibrillation and HF (274). Additionally, the increased presence of hypertension, especially resistant hypertension, in patients with OSA is also tied with LV hypertrophy or increased wall thickness (261).

Insulin resistance, a hallmark of obesity, also participates in the pathogenesis of LV hypertrophy and diastolic dysfunction in obesity. Furthermore, the impact of insulin resistance on LV remodeling and function may be influenced by sex and BMI. In one study, insulin resistance was associated with increased LV mass and LV wall thickness in obese women but not men (275). Indeed, obese women exhibit both eccentric and concentric hypertrophy, whereas obese male counterparts predominantly display concentric hypertrophy. It is well known that concentric hypertrophy serves as a much stronger predictive of CVD mortality compared with eccentric hypertrophy (276). Impaired insulin metabolic signaling plays a predominant role in insulin resistance-elicited LV dysfunction (277). The existence of impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) predisposes the development of LV hypertrophy in normotensive individuals (278).

2.2.3. LA remodeling.

Obesity is often joined with atrial electrostructural remodeling, including alterations in atrial size, conduction, histology (lipodosis), and levels of profibrotic and proinflammatory mediators (279). The accepted methods to evaluate LA size include uniaxial anterior-posterior dimension and LA volume indexed to body surface area or height (280). LA volume is progressively enlarged and corelates well with LV mass (weakly with blood pressure) in obesity (281). However, the reported prevalence of LA enlargement in obese individuals is somewhat variable. This is probably related to the presence of obesity paradox, duration of obesity, the presence of comorbidities, and different methods utilized for body size normalization. For example, the relationship of obesity to LA enlargement is confounded by the

existence of hypertension. Both BMI and BP are risk factors for LA enlargement although BP displays a weaker correlation (282). According to a 10-yr longitudinal study, obesity imposes a stronger clinical relevance than hypertension with respect to LA enlargement (283). Of note, atrial remodeling secondary to obesity is characterized by progressive impairment of atrial structure, electrophysiological function and electro-anatomical integrity, leading to a proarrhythmic status (284).

2.2.4. RV hypertrophy.

Obesity serves as an independent risk factor for RV hypertrophy. Obese individuals display a higher RV mass and larger RV end-diastolic volumes (RVEDV) compared with lean counterparts (76). Indeed, RV mass was 6% and 14% greater, respectively, in overweight and obese groups. These authors noted that every 5 kg/m^2 rise in BMI was associated with a 1.3 g higher RV mass and 8.65 mL higher RVEDV. A significant correlation was identified between BMI and RV mass or RVEDV (285). Assessment of RV wall thickness using echocardiography in normal, overweight, and obese participants has revealed much higher RV free wall thickness in overweight (37 $\pm$ 6 mm) and obese (38 $\pm$ 5 mm for BMI of 30–34.9; 49 $\pm$ 9 mm for BMI $\geq$35) participants compared with lean (33 $\pm$ 6 mm) participants (286).

Factors indicating in RV hypertrophy include OSA and chronic PAH. One study revealed that high-respiratory disturbance index (RDI) is correlated with higher BMI than low-RDI (190). Simultaneously, a significant difference was noted in RV wall thickness between high RDI and low-RDI groups, the effect of which was independent of hypertension and pulmonary function. These findings convincingly support the notion that obstructive sleep apnea might be a link between obesity and RV hypertrophy (287).

Chronic PAH may serve as another independent factor for RV hypertrophy. RV diastolic stiffness is elevated by PAH and is associated with RV disease severity. Histological analyses revealed elevated cardiomyocyte number and RV fibrosis in PAH patients. In addition, RV diastolic stiffness and passive tension at different sarcomere lengths were overtly increased in PAH patients. At the molecular level, phosphorylation of sarcomeric protein titin, an essential governor of sarcomeric stiffening, was overtly lower in RV tissues from PAH group. In this context, increased RV fibrosis may serve as a compensatory mechanism to combat the elevated RV afterload in obesity (288).

2.2.5. Aortic valve stenosis.

Earlier studies have shown conflicting results with regards to the relationship between BMI and aortic valve stenosis (AVS) (289–291). However, recent large cohort observational studies have depicted an association between increased adiposity and AVS risk (292, 293). A Swedish study including 71,817 individuals found a positive relationship between obesity and risk of AVS. Obesity with a BMI $\geq$30 had an 80% higher risk of AVS. Abdominal obesity (waist circumference $\geq$102 cm for men and $\geq$88 cm for women) was tightly correlated with a 30% higher occurrence rate of AVS (292). Later the Denmark group including 108,304 individuals revealed similar results with risk of AVS and aortic valve replacement much greater those with both high BMI and high waist-hip ratio or waist circumference (293). At this point, the precise mechanism behind AVS risk in obesity is unclear although structural or metabolic changes in the heart may play a role. Obesity leads to higher blood pressure that may impose geometric changes on LV and aortic valve (294) as well as damage to endothelial cells (295). Metabolically, elevated plasma lipids lead to lipid deposits on aortic valve leaflets and provoke valvular interstitial damage (295, 296). At the same time, lipid deposition activates inflammatory responses, resulting in differentiation of valvular interstitial cells into osteoblasts and thus calcification of valve leaflets (297).

2.3. Cardiac Dysfunction in Obesity

2.3.1. LV systolic dysfunction in obesity.

Conventional 2-D or M-mode echocardiography is classified as the most common technique for measurement of systolic function by examining stroke volume, ejection fraction, transmitral velocity and fractional shortening. LV EF is reported to be normal (253) or even supranormal in obesity-induced cardiac remodeling (**TABLE 1**), which also underpins the high prevalence of HF with preserved ejection fraction (HFpEF) in obese patients (115). However, increased stroke volume (SV) has been observed in overweight and obese patients, in parallel with increasing levels of fat free body mass (FFM) (191) and CFD (192, 298), indicating elevated systolic load in preclinical obesity cardiomyopathy. Fractional shortening (FS) evaluates circumferential LV myocardial contractility by measuring the percentage change in LV diameter during systole. LV midwall fractional shortening is believed to be more suitable than LV endocardial fractional shortening for the assessment of regional systolic function in LV hypertrophy, particularly concentric geometry. Most studies have demonstrated a slight (261) to moderate (299) decrease of LV midwall factional shortening accompanied by LV hypertrophy in obesity, indicating reduced systolic contraction. To this point, gastric bypass surgery was shown to effectively reverse LV

remodeling along with improved midwall shortening (300).

Notably, ample observations have substantiated subclinical depressed LV systolic function in obesity cardiomyopathy. Although EF can be normal even in severe obesity, longstanding obesity for more than 20 yr is associated with overtly impaired LV systolic and diastolic function (301). Accurate measurements using more sensitive modalities have revealed subclinical systolic dysfunction associated with obesity, as evidenced by proportionally decreased myocardial tissue velocity and strain index with escalating severities of obesity. Myocardial strain typically refers to load-dependent deformation (shortening, lengthening, or thickening) of the myocardium, which is estimated as the ratio of the distances between two points during expansion and contraction (302). Myocardial strain has shown prognostic significance courtesy of the ability to identify subclinical abnormalities in LV and RV function before onset of overt cardiomyopathy and HF (286, 303). This is evidenced by the biventricular strain abnormities that are already present in obese children (302, 304, 305).

Tissue Doppler imaging (TDI), a new echocardiographic modality that detects low-velocity, high-amplitude myocardial motion, has emerged as one of the most widely applied noninvasive tools for the quantitative assessment of myocardial systolic and diastolic function. The TDI-derived parameters of myocardial velocities, including myocardial systolic velocity (Sm, Sa), early diastolic velocity (Em, Ea), late diastolic myocardial velocity (Am), and LV diastolic pressure (E/Em, E/Ea) are already reduced at the preclinical or early stage of cardiomyopathy in obesity (249, 250) and drop further with increased adiposity (249). Tissue Doppler myocardial strain and strain rate imaging are also employed to decipher subclinical cardiac outcomes of isolated obesity. Subclinical cardiac manifestations shown by decreased LV global longitudinal peak strain rate are correlated with BMI, duration of obesity, and increasing age (303). Patients with increasing degree of obesity show diminished myocardial velocity, and strain index, in light of normal ranges of ejection fraction from conventional 2-D echo measurement. These observations indicate diminished LV systolic function even in patients with mild obesity (250).

However, strain measurements based on TDI are angle dependent with the use of the Doppler device which produces simultaneous opposite deformations in the long and short axes. Whereas speckle tracking echocardiography offers more precise and angle-independent readouts of LV dimensions and strains. Speckle tracking relies solely on tracking of characteristic speckle patterns generated by interference of ultrasound beams with myocardial tissues (306). There is evidence suggesting that subclinical LV systolic dysfunction assessed by speckle-tracking global longitudinal strain is associated with abdominal adiposity but not BMI (307).

Another LV derangement found in obesity using speckle tracking echocardiography or MRI is increased LV torsion and untwisting rate. Whether altered LV rotational function is a compensatory machinery for compromised LV contractility or an outcome of insufficient diastolic filling requires further investigation. Systolic torsion and diastolic untwisting are found elevated in the early phases of diastolic dysfunction and are then normalized or reduced in the advanced stage (308). These emerging techniques should help to define earlier cardiac abnormalities associated with overweight and obesity.

2.3.2. LV diastolic dysfunction in obesity.

Diastolic dysfunction develops either alone or in concert with systolic dysfunction and typically precedes the onset of systolic failure (as shown in multiple clinical studies listed in **TABLE 1**). The classic diastolic dysfunction, which denotes abnormalities in relaxation or dampened myocardial compliance, or both, is featured by a higher impedance to LV filling, resulting in an inappropriately elevated diastolic pressure (309). A cross-sectional survey of 1,275 individuals aged 60 to 86 yr found that LV diastolic dysfunction is a common situation among the elderly, although EF is preserved in this setting (270). As it is the case with systolic dysfunction, comprehensive studies using TDI and other techniques have been performed to examine diastolic function in obesity. Current consensus recommends the application of early (E) to late (A) diastolic transmitral flow velocity (E/A) as a surrogate for diastolic function and E to early diastolic mitral annular tissue velocity (E/e') as a more sensitive indicator for LV filling pressures (309). In fact, multivariate analyses demonstrated that BMI is independently associated with higher E, A, and E/e' and even overweight is linked to diastolic dysfunction, as evidenced by reduced E' and higher E/e' in the overweight subjects (310). Obesity in young otherwise-healthy women was found to contribute to concentric LV remodeling and impaired LV relaxation as evidenced by decreased early diastolic myocardial velocity (Em) (249). In addition, hemodynamic data obtained from invasive studies showed that obesity is associated increased LV end-diastolic pressure (298). LV diastolic anomalies appear to be frequent in obese individuals without any clinically evident heart diseases triggered by diabetes mellitus, hypertension, or coronary artery disease.

2.3.3. RV dysfunction in obesity.

Obesity not only leads to RV hypertrophy but also RV dysfunction. Larger RV stroke volume (RVSV) and lower RV ejection fraction (RVEF) are noted in overweight and obese individuals after adjusting for demographics, height, education, and CVD risk factors. Even after adjustment of LV parameters, differences still prevailed. RVSV was increased in overweight and obese individuals. RVEF was mildly but notably lower in overweight and obese individuals (285).

Finally, overtly decreased diastolic and systolic velocities of RV free wall motion were noted in overweight and obese individuals in comparison with lean subjects. Meanwhile, RV systolic and diastolic velocities as well as strain indexes were significantly depressed in overweight and obese individuals in comparison with controls. Alongside with increased BMI, the degree of decline of RV function and strain rate were progressively worsened (286).

2.3.4. Atrial fibrillation.

AF is yet another severe malady commonly seen in obesity. Although the precise etiological nature of obesity-induced atrial arrhythmias remains elusive, LA remodeling manifested by an increased LA dimension may be a key decisive factor. Obesity predisposes to the onset of AF mainly through LA structural and electrophysiological changes, elevated BP, LV hypertrophy, and LV diastolic dysfunction (142, 284). Large ambispective cohort and longitudinal obese ovine findings have revealed that obesity early on in life and progressive weight gain are closely associated with more episodes, prolongation, and greater cumulative duration of AF (311, 312). In a 21-yr cohort study involving 3,248 patients with paroxysmal AF, greater BMI paralleled larger LA volume and predicted incremental progression to permanent AF (313). Based on the electrophysiological findings in LA and pulmonary vein from obese individuals, decreased posterior LA voltage and shortened or unchanged effective refractory period in LA and PVs were found to coincide with elevated LA pressure, LA volume and lower LA strain (314). Infiltration of LA epicardial fat may also serve as a unique substrate for AF in obesity (312). Epidemiological evidence indicates that weight loss greatly lowers AF burden and recurrence incidence following pharmacological treatment in obese patients (163). The Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study denoted one of the largest multicenter clinical trials for AF, involving 4,060 patients. Although earlier reports noted an association between obesity and higher risk of AF, multivariate analysis from AFFIRM study found an interesting "obesity paradox" for AF outcomes, where overweight and obesity were in fact related to a decreased all-cause mortality (315).

2.3.5. Clinical HF and obesity.

Uncorrected obesity is a major culprit factor for heart failure (HF), independent of other CVD risk factors, including diabetes mellitus, ischemic heart diseases, dyslipidemia and hypertension. In the international cohort study of international Sarcomeric Human Cardiomyopathy Registry (SHARE) with a median follow-up of 6.8 yr, BMI >30 was independently correlated with HF and arrhythmias irrespective of genotype, age and sex (155). Clinical manifestation and pathophysiology are often redundant between obesity and HF, including decreased LV function, cardiac remodeling, neurohormonal activation (sympathetic nervous system and RAAS). Obese patients are commonly characterized by reduced exercise capacity, increased cardiac filling pressure, Na retention, plasma volume expansion, and a normal LV ejection fraction. These individuals exhibit one of the three following phenotypes. First, HF in obesity occurs in association with hypervolemia, including Na retention, plasma volume expansion, and cardiac enlargement, although cardiac index and circulating levels of natriuretic peptides are not significantly elevated. It is believed that RAAS activation and increased aldosterone levels may underscore hypervolemia in obesity (175, 185). In addition, increased leptin levels directly activate both RAAS and sympathetic nervous system (179, 185). Second, elevated natriuretic peptides in obesity lower systemic vascular resistance, leading to LV dilatation, increased RV and LV filling pressures, resulting in high-output HF and glomerular hyperfiltration (188). This is consistent with increased LV end-diastolic pressure in obesity, indicative of diastolic dysfunction (95). LV and possibly RV dilation are likely a result of increased CO in obesity. In subpopulations of obese patients, elevation of natriuretic peptides may contribute to decreased systemic vascular resistance and elevated CO (175, 316). Endogenous natriuretic peptides are normally constrained by neprilysin produced by adipocytes (317). However, the release of natriuretic peptides greatly exceeds the degradative capacity of adipocyte-related neprilysin with continuous stretch of ventricles, resulting in systemic vasodilatation and high output HF (188). In addition, increased natriuretic peptides may result in glomerular hyperfiltration due to low afferent arteriolar resistance in obesity-related high output HF (318). Third, it has been noted that older female obese patients often exhibit HFpEF with modestly elevated ventricular dimensions, frequent AF, increased natriuretic peptides and glomerular malfunction and plasma

volume expansion reminiscent of high output HF (183). As the LV dilates wall stress rises thereby prompting secondary eccentric hypertrophy. With proportionated LV hypertrophy in response to ventricular dilation, systolic function remains preserved (due to normalized wall stress), resulting in the onset of HFpEF. If LV hypertrophy is unable to keep pace with dilation (inadequate hypertrophy), LV wall stress overtly rises to promote systolic dysfunction (319, 320). In this context, obesity is deemed a primary factor for the etiology of HFpEF (321, 322). To distinguish among these three phenotypes and optimize therapeutic interventions in obese individuals, several key parameters may be used including exercise intolerance, rises in ventricular filling pressures, and LV ejection fraction. In particular, recognition of HF in obesity is urgently needed to initiate large-scale clinical trials enrolling obese patients with various forms of HF.

2.4. Obesity Paradox

Emerging evidence suggests that overweight or obesity is associated with an improved survival in patients afflicted with CVD (175, 323, 324). In general, HF patients who are underweight display the highest cardiovascular mortality and hospitalization prevalence, as opposed to those who are overweight or obese (324, 325). This is profoundly noted in epidemiological findings with a better prognosis in obese patients with HF, a phenomenon termed "obesity paradox" (167). Not only does obesity paradox exists in HF, intervention cardiac procedure such as percutaneous coronary intervention (PCI) also exhibits a much lower mortality rate in overweight and obese patients in comparison with lean subjects (166).

2.4.1. Potential rationales underlying obesity paradox.

Several scenarios may be considered for obesity paradox. First, the severity of HF may be overestimated in obese patients because of the concurrent comorbidities such as dyspnea (171). Second, nearly all available data concerning "obesity paradox" at this point use BMI as the gold standard to categorize obesity. In this regard, 60,335 participants were followed up for 10 yr comparing BMI with body composition indices as predictors of CVD death. The results yielded a stronger association between BMI and CVD mortality (326). However, compared with other adiposity measures, BMI does not accurately reflect various cardiometabolic risks in obesity since it cannot distinguish fat mass from fat-free mass (327, 328). Lower FFM is pertinent to increased risk of death in the lower BMI range (329, 330). Measurement for abdominal obesity using waist-to-height ratio (WHR) and waist circumference (WC) should better pinpoint fat mass and decipher cardiometabolic risks associated with obesity (331). Independent of BMI, abdominal obesity is associated with impaired LV contractile and diastolic function and associated with higher mortality risk in adults (251, 307, 332). Furthermore, increased pericardial fat is related to the pathogenesis of obesity-related CVDs and displays a stronger correlation with heart structure and function than the more general obesity indicators (333).

2.4.2. Other risk factors of CVD outcomes in obesity.

Obesity is often a product of intertwined nutritional and lifestyle risk factors including smoking (334). A population-based study noted escalating prevalence and mortality of CVD with increasing BMI in diabetic patients following exclusion of smoking, poor metabolic control, and short duration of follow-up (126). The relationship between BMI and CVD incidence is more linear in subgroups without any comorbidities or smoking (335), whereas the increased risk of death in underweight (J-shape association) is apparent in ever smokers in a subgroup analysis of smoking status (336). Sex differences also impact the correlation between obesity and CVD outcome. For instance, increased abdominal fat, assessed by WHR, seems to be tied with a higher mortality risk in female but not male HF patients (160). Cardiorespiratory fitness (CRF) is a measure of how well the lungs and CV system perform during physical activity (168). High CRF has long been considered a predictor of lower CVD risks and better prognosis (168, 337), while low CRF results in greater impairment in LV strain (338) and chronic disability due to CVD (339). The obesity paradox was less pronounced among diabetes patients with high CRF, although mortality risk decreased with increasing BMI in patients with low CRF (173).

Furthermore, emerging evidence has started to shed light on the existence of the heterogeneity in obesity as defined by BMI. The metabolically healthy obese (MHO) refers to an obesity trait in the absence of dyslipidemia, insulin resistance, hypertension, diabetes mellitus, and any of the classical cardiometabolic factors, conferring less prevalence for CVD (340). However, previous studies have provided inconsistent results about the association of MHO and CVD. In fact, a large proportion of MHO may be converted to an unhealthy phenotype over time with an associated higher CVD incidence compared with a normal-weight group (341). Therefore, MHO should not be considered as healthy, as existing clinical approaches can hardly identify a "stably" benign obese subgroup (342).

3. BASIC MECHANISM OF OBESITY CARDIOMYOPATHY

3.1. Adipose Tissue Dysfunction and Inflammation

Obesity is characterized by chronic activation of inflammation, commonly associated with and a contributing factor for insulin resistance and T2D (104, 343, 344). Ample recent evidence has depicted an important role for dysfunctional adipose tissues in inflammation, insulin resistance and cardiac abnormalities. Obesity is a progressive pathological process whereby adipocytes and resident immune cells are activated and subsequently release vast secretory factors. In addition, various immune cells are recruited to adipose tissues, where they are converted into an active inflammatory phenotype to produce and release proinflammatory cytokines (343). Ample evidence has revealed an essential role for alterations in these adipose tissue-released factors, termed adipocytokines, including adiponectin, leptin, resistin, nitric oxide, interleukins, tumor necrosis factor-α (TNF-α), and other inflammatory mediators in the development of CVD via an autocrine, paracrine or endocrine fashion (**FIGURE 4**). Other local and systemic influences, such as insulin resistance (IR), renin-angiotensin-aldosterone system (RAAS) activation, lipotoxicity, and interstitial fibrosis, may act in synergy with adipocytokines in the onset and development of CVD.

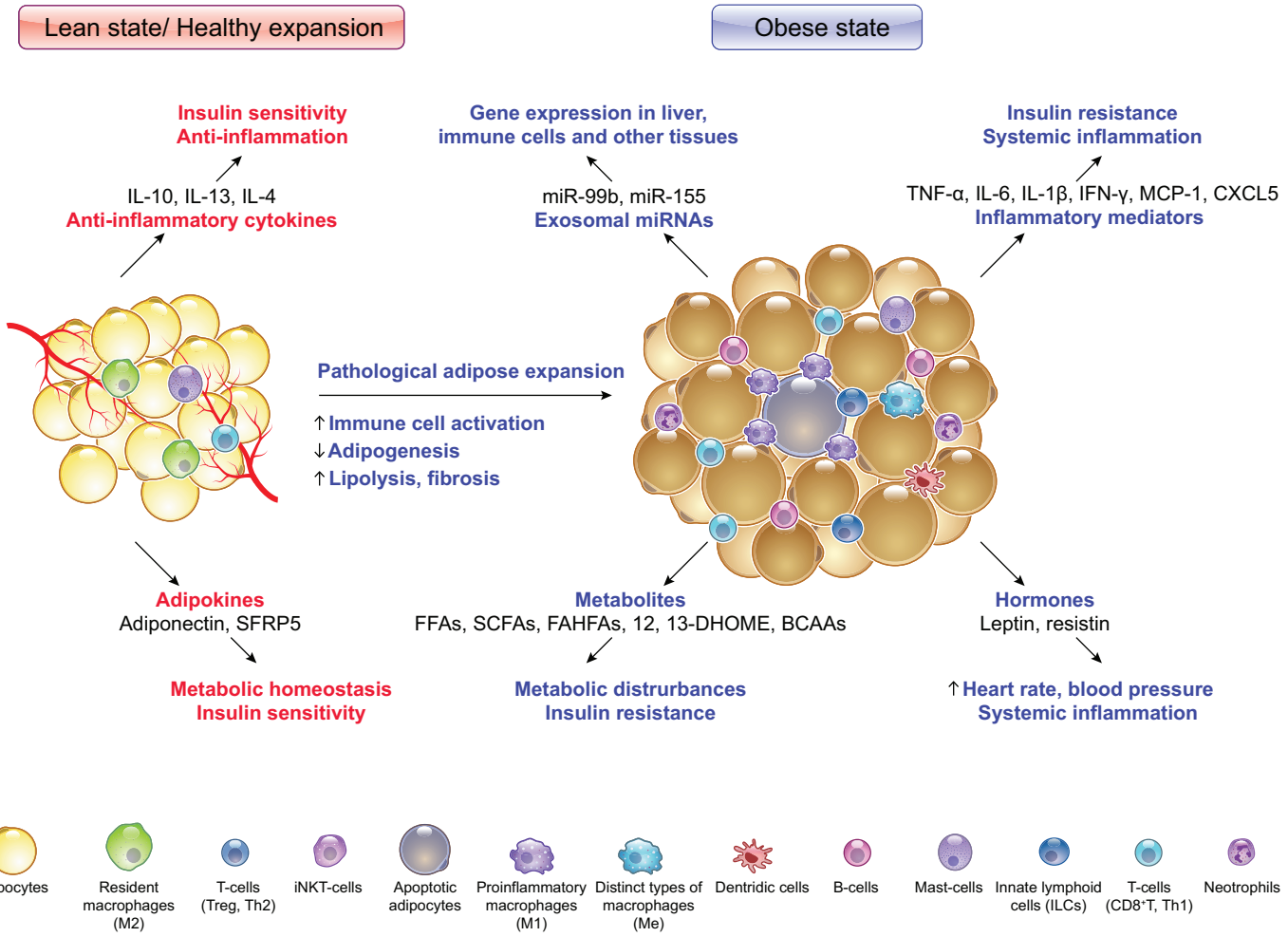


FIGURE 4. Adipose tissue dysfunction and inflammation in obesity that directly and indirectly aggravates cardiomyopathy: In lean state, adipocytes secrete various endocrine factors that maintain metabolic homeostasis. In response to chronic energy excess, infiltration of proinflammatory immune cells and hypertrophic adipose expansion along with a lack of adipogenesis can be observed in adipose tissues, which is accompanied by altered secretion of adipose tissue hormones, cytokines, metabolites, and exosomal miRNAs. Overall, the changes in hypertrophic adipose tissue contribute to insulin resistance, impaired glucose, and lipid metabolism and low-grade systemic inflammation and exert local effects that exacerbate cardiomyopathy in obesity. IL-10, -13, -4, interleukin 10, 13, 4; SFRP5, secreted frizzled-related protein 5; TNFα, tumor necrosis factor-α; IL-6, -1β, interleukin 6, 1β; IFN-γ, interferon γ; MCP1, monocyte chemoattractant protein 1; CXCL5, C-X-C motif chemokine ligand 5; FFAs, free fatty acids; SCFAs, short-chain fatty acids; FAHFAs, fatty acid esters of hydroxy fatty acids; 12,13-DHOME, 12,13-dihydroxy-(9Z)-octadecenoic acid; BCAAs, branched-chain amino acids. Created with BioRender.com.

3.1.1. Ectopic adipose tissue in obesity cardiomyopathy.

There exist two main kinds of adipose tissues, white adipose tissue (WAT) and brown adipose tissue (BAT), among which WAT is predominant in mammals while BAT resides in several regions such as interscapular and supraclavicular areas (345). Adipose tissues can also be divided into different anatomical depots, VAT, and subcutaneous adipose tissue (SAT) (346). Adipose tissue dysfunction, especially WAT dysfunction, plays an imperative role in the pathogenesis of various metabolic diseases and CVDs (133).

3.1.1.1. PATHOLOGICAL FEATURES OF ADIPOSE TISSUE IN OBESITY. The expansion of adipose tissue includes hyperplasia/adipogenesis (new adipocytes differentiated from precursor cells) and hypertrophy (the increase in adipocyte size) (347).

Interestingly, pathological expansion of adipose tissue in obesity is accompanied with a decline of hyperplasia and adipogenesis (347, 348). Subcutaneous adipose tissue (SAT) serves as the largest reservoir for lipid storage that prevent excess lipids accumulating in peripheral organs such as liver, heart, and muscles in physiological conditions. The limited expansion and dysfunction of SAT due to impaired adipogenesis lead to a hypertrophic expansion of adipose cells and increased fibrosis in adipose tissue (348–350). Hypertrophic adipose depots present different biochemical properties, including elevated lipolysis, increased secretion of inflammatory cytokines, and reduced secretion of anti-inflammatory adipokines (351, 352). Lipotoxicity caused by excessive hypertrophic fat accumulation leads to insulin resistance and functional deficits in both adipose tissue and other organs including liver, heart, muscle, and pancreas (164, 344, 353, 354).

Insulin resistance is regarded as a springboard linking adipose tissue accumulation in obesity to CVD. Although inflammation of adipose tissues is required for physiological expansion of adipose tissues in healthy individuals, evidence from both clinical and experimental studies strongly suggests an important relationship between systemic inflammation caused by maladaptive adipose tissues and insulin resistance in obesity (355).

3.1.1.2. ECTOPIC FAT DEPOSITION. As SAT fails to store excess fat, lipids accumulate in visceral adipose tissues and other tissues, which would normally contain only small fractions of fat, including liver, skeletal muscle, heart, and pancreas (356). Certain ectopic fat depots, such as vascular adipose tissue (357), intrahepatic fat, and intramuscular fat, predominantly generate systemic effects (358), while adipose tissue surrounding heart [epicardial adipose tissue (EAT) and paracardial adipose tissue (PAT)] and most of the blood vessels (PVAT) are pertinent to adverse local CV effects (357, 359).

Adipose tissues surrounding the heart are classified into two layers: epicardial adipose tissue (EAT) and paracardial adipose tissue (PAT) based on anatomic location. EAT is the fat depot between myocardium and pericardial visceral layer and is anatomically and functionally contiguous with myocardium (360). Paracardial fat is located outside of the visceral pericardium. Perivascular adipose tissue (PVAT) refers to adipose tissue surrounding blood vessels, which plays a key role in the maintenance of vascular function. PVAT normally possesses antiatherogenic functions by secreting biologically active factors (361, 362). However, PVAT becomes dysfunctional in obesity with an increased level of proinflammatory adipokine secretion, which induces oxidative stress in vessels and leads to endothelial dysfunction, impaired vasodilation, and stiffening of vessels. All of these events may lead to vascular dysfunction and CVD (361, 363).

3.1.2. Local effects of EAT.

EAT is a marker of visceral adiposity and cardiac lipotoxicity and sets the stage for cardiac dysfunction in adiposity by promoting inflammation and metabolic disorders in the heart (364, 365). Epicardial fat directly exerts local effects on cardiac structure and function, including elevated LV mass, deranged RV geometry, and impaired relaxation (366, 367). Of note, therapeutic interventions targeting adipokines greatly reduce the risk of heart failure, while drugs promoting accumulation of epicardial adipocytes or inflammation may exacerbate CVD, including AF, coronary artery disease, and HF (365, 368).

Both mechanical and biomolecular factors may underlie the impact of EAT on heart structure and function (367). First, increased EAT puts additional mechanical stress on both ventricles and increases cardiac workload, leading to LV hypertrophy. In addition, increased EAT also exaggerates atrial enlargement and ventricular diastolic dysfunction owing to physical obstruction of cardiac filling. Second, infiltration of adipocytes from EAT to the myocardium facilitates aberrant cardiac metabolism by promoting excessive myocardial FFA usage and development of lipotoxicity. Third, in obesity, EAT is enriched with a transcriptome associated with genes governing inflammation, and endothelial dysfunction (364, 369). EAT serves as a local transducer of systemic inflammation to the myocardium and a source of local secretion of proinflammatory adipocytokines that promotes myocardial disarray, cardiac fibrosis, and stiffness in uncorrected obesity. As the metabolic profile shifts in obesity and EAT abnormally expands, both resident

and infiltrated immune cells generate a proinflammatory microenvironment with cardiomyocytes, which influents cardiac metabolism and contractility (344, 360). In addition, increases in EAT was shown to elicit local electromechanical responses in atrial tissues though released cytokines, such as TNF and IL-6, as well as FFAs.

3.1.3. Systemic effects of adipose tissue.

Adipose tissue is considered an endocrine organ and an "ancestral immune organ" (110, 370, 371). Generally speaking, adipokines are hormones, metabolites, exosomal microRNAs, cytokines and chemokines secreted by adipose tissue and sent to the targets in other organs, such as adiponectin, leptin, resistin, FFA, transforming growth factor-β (TGF-β), interleukins, fibroblast growth factor 21 (FGF21), bone morphogenetic protein (BMP)-4, BMP-7, and many others (370, 372). Obesity is characterized by a decrease in anti-inflammatory adipokines and an increase in proinflammatory ones. This shift impacts on multiple functions such as appetite, energy balance, endothelial function, and immunity, promoting the development of chronic, systemic inflammation, and insulin resistance, processes that are thought central to the obesity-associated CVD (344, 373).

3.1.3.1. DYSREGULATION OF ADIPOKINES. 3.1.3.1.1. Decreased anti-inflammatory adipokines. Adiponectin is one of the principal adipokines with insulin-sensitizing and anti-inflammatory properties. Plasma levels of adiponectin are declined in obesity (374–377). In a study of 933 middle-aged subjects, low plasma adiponectin levels were independently correlated with increased LV hypertrophy (378). Adiponectin evokes cardioprotection against pathological cardiac remodeling and ischemia injuries partially through reducing myocardial oxidative stress, suppressing inflammation, and improving energy supply (379). Although clinical studies are limited, these cardioprotective effects are potentially translational.

Secretion of cardiac FGF21 is increased in response to obesity to evoke cardioprotection (380), while FGF21 deficiency predisposes the susceptibility of obesity-related cardiomyopathy in mice (381). Interleukin 10 (IL-10) is generally considered as an anti-inflammatory cytokine. As IL-10 levels are declined in obesity, systemic IL-10 administration was found to markedly ameliorate LA remodeling and vulnerability to AF in diet-induced obesity (382). Interleukin 33 (IL-33), another anti-inflammatory adipokine from the IL-1 family, participates in type 2-like immune responses (383, 384). Levels of IL-33 were suppressed in obesity and were correlated with natriuretic peptides in hearts (385). Secreted frizzled-related protein 5 (SFRP5) is another anti-inflammatory adipokine secreted from WAT and suppresses inflammation in WAT (386, 387). FAM19A5, a novel adipokine, inhibits neointimal formation through sphingosine-1-phosphate receptor 2-G12/13-RhoA signaling (388, 389).

3.1.3.1.2. Increased proinflammatory adipokines. Dysfunctional adipose tissue in obesity releases an abundance of proinflammation factors, including leptin, resistin, chemokine, and cytokines such as transforming growth factor-α (TNF-α), interleukin-6 (IL-6), IL-1, and monocyte chemoattractant protein-1 (MCP-1) (390).

Leptin, a 16-kDa peptide hormone product of the ob gene, is one of the proinflammatory adipokines secreted by adipocytes (391). The level of leptin is elevated in obesity to coincide with cardiac hypertrophy through binding of leptin to the short form leptin receptor in rat hearts (392). The adiponectin/leptin ratio is a marker for adipose tissue status, exhibiting an inverse correlation with low-grade chronic inflammation (393). Leptin deficiency mitigates diet-induced and preestablished obesity through polarizing macrophages to anti-inflammatory phenotypes, while hyperleptinemia is frequently accompanied by insulin resistance, T2D, and increased prevalence of CVD (394).

Resistin is an adipokine secreted by macrophages within adipose tissues in obesity. Increased levels of resistin in obesity mediate LV hypertrophy (252) and systolic dysfunction (395) possibly through fostering contractile dysfunction (396), inflammation, and endothelial activation (397). However, the precise role of resistin remains unclear in obesity as experimental evidence either failed to confirm the association between resistin and obesity (398) or favored dissociation between insulin resistance and elevated resistin levels in obesity (334).

Levels of TGF-β1 were overtly increased in LV from obese compared with lean rabbits, possibly contributing to cardiac collagen deposition (399). IL-6 deficiency promotes insulin resistance and cardiac lipid accumulation, interstitial fibrosis, and inflammation in high-fat diet-induced obesity (400). C-X-C motif chemokine ligand-14 (CXCL14) is an adipokine secreted in BAT, which mediates the communication between brown fat and macrophage in response to thermogenic activation (401). Osteopontin (OPN) is another proinflammatory cytokine abruptly elevated in adipose tissue from obese individuals. OPN functions as a key mediator in promoting macrophage proliferation for local adipose tissue in obesity (402, 403). Endocannabinoids, another proinflammatory adipokine, have an important role in regulating energy intake, storage, and consumption (404). Leukotriene B4 (LTB4) facilitates the development of insulin resistance in a macrophage-dependent manner in obesity (405).

3.1.4. Activation of immune cells.

As discussed above, adipocytes can become inflamed and secrete a variety of inflammatory adipokines. However, with the identification of macrophages in adipose tissue (AT), activation of immune cells is known to promote the release of the majority of inflammatory molecules in obese animals and humans (**FIGURE 4**). Adipose tissue macrophages (ATMs) possess a vital role in this process and can be divided into two main phenotypes, including M1, the classically activated macrophages, and M2, the alternatively activated macrophages (406).

3.1.4.1. M1/M2 PARADIGM IN OBESITY. Generally speaking, M2 macrophages produce anti-inflammatory adipokines and help maintain AT homeostasis in the lean state by playing an important role in phagocytosing necrotic or apoptotic myocytes, tissue remodeling, and cardiac fibrosis after injury (407, 408). On the other hand, the number of AT M1 macrophages rises in obesity and correlates with AT inflammation and insulin resistance as mediated by increasing proinflammatory cytokines (350, 406, 409). Macrophages ranges from under 10% in AT in lean mice and humans, the levels of which may exceed 40%–50% through local proliferation (410) and infiltration in obese humans and leptin-deficient obese rodents (411).

EAT can be a major source of cardiac M1 macrophages, thereby contributing to cardiac anomaly- associated obesity. In addition, resident macrophages exist in the healthy heart in low numbers, where they typically assume an M2 phenotype but can be inflamed during obesity (412). Cardiac macrophages expand in humans and mice with diastolic dysfunction owing to monocyte recruitment and hematopoiesis in bone marrow and spleen (413). The systemic and cardiac inflammation associated with obesity and pathological cardiac remodeling is largely mediated by M1 macrophages (412).

Although accumulation and activation of immune cells has been extensively reported in obesity, the signals that trigger and magnify these inflammatory changes remain to be deciphered. A number of scenarios are speculated for obesity-linked inflammation including hypoxia, adipocyte and cardiomyocyte death, gut microbiota, and alternation of circulating metabolic substrates, which help to program metabolic, inflammatory, and functional traits of AT immune cells (344, 414–422).

3.1.4.2. ROLE OF MACROPHAGES IN OBESITY-INDUCED CARDIOMYOCYTE HYPERTROPHY AND DYSFUNCTION. Macrophages mediate LV inflammation and remodeling through several perceived mechanisms. First, macrophages promote pathological hypertrophy and impair systolic and diastolic function in the heart through proinflammatory cytokines (TNF-α, IL-1β, IL-6, IL-12, and IL-23), which in turn stimulate mitogen-activated protein kinase (MAPK) and NF-κB signaling and inhibit the Akt-mechanistic target of rapamycin kinase (mTOR) cascade in neighboring cardiomyocytes (412, 423). Second, macrophages secrete matrix metalloproteinases (MMPs) to degrade extracellular matrix (ECM) and phagocytose necrotic cardiomyocytes. Macrophages promote myocardial stiffness and indirectly compromise myocardial relaxation through activating fibroblasts and promoting collagen deposition as well as secreting ECM proteins (412, 413). Third, M1 macrophages also exacerbate systemic complications of cardiometabolic syndrome, including insulin resistance and hypertension through a cascade of cytokines (412, 414, 424, 425). Last but not least, the lipid-buffering capacity and lipolysis become defective in obese adipose tissue macrophages (ATMs), leading to excessive lipid release into the bloodstream and subsequently development of cardiac lipotoxicity (409, 426).

Taken together from the aforementioned findings, macrophage is a promising target to prevent and mitigate obesity-induced cardiomyopathy. Ezetimibe, a potent cholesterol absorption inhibitor, mitigated interstitial fibrosis and coronary arterial thickening in the heart through ameliorating cardiac macrophage infiltration in db/db mice (427). Mineralocorticoid receptor (MR) inhibition using a low-dose spironolactone (LSp) specifically increased M2 macrophage and attenuated inflammation in the heart, leading to restored diastolic function and lessened fibrosis in the heart (428).

3.1.4.3. OTHER IMMUNE CELLS IN OBESITY. The phenotypic switch of AT macrophages may be more complex than the classical M1–M2 paradigm. Multiple phenotypes along the M1/M2 spectrum exist, each with potentially distinct functions, phenotypes, and markers (429, 430). Fatty acids (FAs) are believed to function as a main drive for metabolic activation of ATMs in obese adipose tissue. Alterations in lipid metabolism may be predominantly responsible for inflammatory activation in metabolically activated macrophages (431). Evidence from human subcutaneous adipose tissue (SAT) revealed that fat mass enlargement is associated with accumulation of CD206+/CD16- macrophages, which exert a pronounced proangiogenic response on AT-derived endothelial and progenitor cells, and various cardiovascular pathologies (432).

In addition to macrophage, several other Immune cells are highlighted as important factors in inflammatory responses that may impact global energy metabolism. For instance, natural killer (NK) cells, mast cells, and

innate lymphoid cells (ILCs) as well as the cytokines derived from them are necessary to foster polarization of proinflammatory macrophages and obesity-associated insulin resistance and metabolic complications (433–435), whereas, invariant NK T cells, conventional dendritic cells, and the associated Cd40 signaling pathway are poised to counteract obesity-induced inflammation and promote the immunometabolic status in heart (436–438).

3.1.5. Insulin resistance and inflammation cross talk in obesity.

While insulin resistance seems to precede and contribute to AT inflammation (439), most studies support that inflammation, in addition to caloric imbalance, may impose a culprit role in the pathogenesis of insulin resistance (344, 418, 424, 440).

3.1.5.1. THE IKK/NF-κB PATHWAY. It has been suggested that activation of IKKβ/NF-κB signaling cascade fosters insulin resistance through IKK-mediated serine phosphorylation of insulin receptor substrate 1 (IRS-1) or insulin receptor (IR) (441), which results in compromised tyrosine phosphorylation of IR1-1 and postreceptor signaling molecules such as glucose transporter type 4 (GLUT4), resulting in insulin resistance (440, 442).

Surprisingly, although adipose-specific TANK binding kinase 1 (TBK1) deficiency attenuates high-fat diet-induced obesity, it promotes activation of nuclear factor-κB (NF-κB), with upregulation of MCP-1 production from adipocytes and macrophage infiltration into adipose tissue, associated with worsened insulin resistance in high-fat diet-fed mice (441). To this point, Amlexanox, an inhibitor of noncanonical IκB kinases IKKε and TBK1, overtly lowered Hemoglobin A1c and improves insulin sensitivity in a subgroup of obese patients (443).

3.1.5.2. THE NLRP3 CASCADE. The canonical NF-κB pathway is initiated by the activation of the pattern recognition receptors (PRRs). The Nod-like receptor (NLR) family of PRRs represented by NLRP3 inflammasome serves as innate immune sensors and participates in the recognition of "danger signals," resulting in caspase-1 activation and release of interleukin-1β (IL-1β)/IL-18. A rise in body weight in patients, sheep, and mice has been shown to be accompanied with NLRP3-inflammasome activation in the heart and other organs (444, 445). Antiobesity measures such as caloric restriction and exercise were shown to lower levels of adipose NLRP3, suppress inflammation, and improve insulin sensitivity in obesity. In response to lipotoxicity mainly manifested as intracellular ceramide rise, NLRP3 inflammasome promotes caspase-1 cleavage in macrophages and adipose tissue. This is supported by ablation of obesity-associated inflammasome activation in liver and fat depots along with improved insulin signaling with NLRP3 knockout (446). In the heart, NLRP3 ablation resisted pacing-induced AF in the face of high-fat intake, denoting a key role for NLRP3 inflammasome in obesity-induced atrial arrhythmogenesis (444). In another independent study, although deficiency of NLRP3 and the adaptor protein apoptosis-associated speck-like protein containing CARD domain (ASC or Pycard) retarded obesity-induced systemic inflammation, LV concentric remodeling and diastolic dysfunction without affecting cardiac hypertrophic response to high-fat diet-induced obesity. In addition, deficiency in NLRP3 and ASC was found to protect against obesity-induced metabolic derangement including compromised insulin signaling and steatosis in hearts and livers (445).

3.1.5.3. TOLL-LIKE RECEPTORS: TLR2 AND TLR4. Toll-like receptors (TLRs), another major family of PRRs, plays a critical role in early innate immunity by recognizing the pathogen-associated molecular patterns as well as endogenous damage-associated molecular patterns (DAMPs). Intake of high-energy Western diet (high refined carbohydrates and saturated fat) has been shown to elicit adaptive pancreatic β-cell proliferation to offset peripheral insulin resistance. Interestingly, both TLR2 and TLR4 may suppress high-fat diet-induced replication of β-cells. When both receptors are removed, replication of β-cells but not α-cells is activated resulting in expanded β-islets and hyperinsulinemia in diet-induced obesity (447).

3.1.5.4. C-JUN-NH_2-TERMINAL KINASE AND MAPK. C-Jun NH_2-terminal kinase (JNK) and other mitogen-activated protein kinases (MAPKs), such as p38 MAPK, are activated in response to stress stimuli including saturated FAs, IL-1β, TNFα, and endoplasmic reticulum (ER) stress, to promote insulin resistance through serine and threonine phosphorylation of IRS, as well as dampened downstream postreceptor signaling (344, 440). In particular, immunophenotyping examination indicated a vital role for JNK activation in proinflammatory macrophage polarization (448).

3.2. Metabolic Disturbances

3.2.1. Insulin resistance.

The term "insulin resistance" (IR) commonly makes reference to a decline in metabolic response to insulin in target cells, or at the whole-organism level, demand of higher insulin levels to reduce blood glucose (449). Insulin sensitivity denotes the capacity of insulin to bind

insulin receptor and evokes intrinsic tyrosine kinase activity of the receptor, leading to phosphorylation of IRS1/2 and activation of phosphatidylinositol-3 kinase (PI3K) and MAPK (450). IRS-1/IRS-2-mediated activation of PI3K mediates metabolic actions of insulin (i.e., increasing glucose uptake), whereas MAPK pathway (Grb2/Sos/Ras/ERK) mainly governs growth and remodeling responses in the heart. In addition, insulin also participates in the regulation of fat metabolism such as suppression of fatty acid oxidation (FAO) (449, 450). A number of postreceptor components, including serine/threonine protein kinase Akt, protein tyrosine phosphatase 1B (PTP1B), and mammalian target of rapamycin (mTOR), have been reported to mediate insulin-induced glucose metabolism (451–453).

Loss of insulin sensitivity or IR represents a cardinal trait of obesity and T2D and contributes to onset and development of heart diseases. The heart is an important insulin responsive organ and can become insulin resistant in obesity (454, 455). Given the key role of insulin as the predominant anabolic hormone in growth, development, glucose, protein, and lipid metabolism, insulin resistance is known to directly provoke adverse cardiovascular sequelae in obesity. Of note, metabolic milieu in the setting of insulin resistance is featured by elevated circulating levels of glucose, free fatty acids, and triglycerides, as well as dysregulated substrate supply from the periphery to the heart, along with elevated fatty acid oxidation, decreased glucose uptake and oxidation, and altered gene expression in cardiomyocytes (456). Compromised insulin-stimulated glucose uptake and dampened postinsulin receptor signaling have been considered a hallmark in the hearts from obese individuals, to various degrees pending on severity and duration of adiposity.

3.2.1.1. EVIDENCE FOR INSULIN RESISTANCE IN OBESITY. Ample evidence has depicted the presence of insulin resistance preceding the onset of LV remodeling and contractile dysfunction in obesity, favoring a vital role for insulin resistance in the pathogenesis of obesity cardiomyopathy. Not surprisingly, insulin resistance cardiomyopathy shares many commonalities with obesity cardiomyopathy.

Mounting findings have denoted a cardinal role for systemic insulin resistance in the etiology of cardiac dysfunction in patients with obesity. This theory is convincingly supported by the presence of insulin resistance in obesity whereas all adiposity measures (e.g., BMI, waist circumference, skinfold thicknesses, and bioimpedance) are positively correlated with the insulin sensitivity marker homeostatic model assessment for insulin resistance (HOMA-IR) (275, 457). In CARDIA (Coronary Artery Risk Development in Young Adults) study involving 3,179 patients, changes in HOMA-IR were monitored in nondiabetic populations based on severity of insulin resistance (low IR, moderate IR, and high IR). It was noted that severe form of IR in early adulthood was closely associated with accentuated LV wall thickness and worse longitudinal systolic strain, as well as early diastolic strain rate at middle age, depending on the severity of obesity (458). In addition to insulin resistance, glucose intolerance represents another key denominator for LV dysfunction. Examination of LV parameters and glucose tolerance in 2,623 Framingham Study individuals (in the absence of myocardial infarction and heart failure) revealed a tight correlation between glucose intolerance and LV mass/wall thickness, with a more pronounced effect in women than men. Adjustment for BMI considerably weakened the correlation between LV/LA parameters and HOMA-IR, with nonsignificant finding in the normal glucose tolerance group (275). Indeed, patients with both impaired IFG and IGT displayed greater LV mass, LV mass index, and lower Doppler early peak rapid filling velocity to peak atrial filling velocity ratio compared with those individuals with IFG alone, exhibiting a 10-fold higher susceptibility of preclinical LV hypertrophy. LV mass index was associated with WC, C-reactive protein, and 2-h oral glucose tolerance test (278).

Cardiac insulin resistance, on the other hand, dampens cardiac metabolism and function in obesity. A decline in insulin-stimulated cardiac glucose metabolism was observed much sooner in response to obesity in comparison with that in skeletal muscles, adipose tissues, and liver (roughly 1.5 wk vs. 3 wk after the initiation of high-fat feeding) (454). This suggests that obesity-induced cardiac dysfunction may be attributable to local insulin resistance and changes in cardiac metabolism rather than the global systemic insulin resistance (454). The same study also reported reduction in Akt-mediated insulin signaling and GLUT4 levels in cardiac insulin resistance (454). However, a later study offered contrary finding where increased cardiac glucose uptake; enhanced mitochondrial oxidation of palmitoyl carnitine, glutamate, and succinate; and greater basal insulin signaling were present in high-fat diet-fed mice compared with those of chow-fed mice, despite the presence of systemic insulin resistance (459). Given the high metabolic dynamics in the heart, different pathways may be involved in the response to hyperinsulinemia in the heart. In fact, it was shown that IGF-1 receptor-mediated Akt activation promoted cardiac hypertrophy in ob/ob mice and mTOR was responsible for the suppression of autophagy flux through alternative upstream pathways such as ERK signaling but not Akt (451, 460).

3.2.1.2. METABOLIC MEDIATORS OF INSULIN RESISTANCE. A number of scenarios have been speculated for insulin resistance in obesity, with positive energy balance as a

result of high caloric intake and low physical activity being the most important factor. However, caloric imbalance cannot fully address the multifaceted metabolic traits in insulin resistance. Accumulating evidence has suggested a rather important role for altered inter-organ communication using various metabolites as messengers in insulin resistance. Of note, targeted and untargeted metabolomics have significantly enriched our knowledge of the role of lipids, amino acids and glucose in promoting insulin resistance (461).

3.2.1.2.1. Lipids. Hypertrophic adipocytes become resilient to the antilipolytic action of insulin and impose a reduced ability to lipid storage, leading to accumulation of fat in, inter alia, muscle and liver cells, (461). More than five decades ago, Randle and colleagues (462) reported that lipids can provoke insulin resistance in diaphragm and hearts. Later studies confirmed that ectopic deposition of fatty acids and lipid metabolites, such as long-chain acyl-CoA esters, diacylglycerol (DAG), triacylglycerol (TG), and ceramide in muscles is closely related to the onset and development of insulin resistance (463–465). Schulman and colleagues (466) also revealed similar mechanism for diacylglycerol-induced insulin resistance in the liver through PKC-ε activation and decreased IRS-2 tyrosine phosphorylation. More recently, beneficial properties of certain lipid categories on insulin signaling have emerged, such as gut microbiota-generated short-chain fatty acids (acetate, propionate, and butyrate) (467), dietary unsaturated fatty acids (468), fatty acid esters of hydroxyl fatty acids (469), and phospholipids.

3.2.1.2.2. Amino acids. The circulating levels of amino acids (AAs) are tightly correlated with insulin resistance in obese humans (461). In particular, branched-chain AAs (BCAAs), representing ~20% of protein intake, aromatic AAs, and certain AA metabolites have garnered attention as to their role in insulin resistance. BCAAs offer various physiological and metabolic benefits including stimulation of pancreatic insulin secretion, adipogenesis, milk production, and immune function. Elevated serum BCAA levels were reported in obesity and insulin resistance decades ago (470). Following its initial perceived pathophysiological role as a reliable marker for obesity and T2D (471, 472), more studies have surfaced implicating a vital role for dysregulated BCAAs in the etiology of other chronic diseases such as cancers (473) and CVD (474), possibly mediated by the development of T2D. BCAAs are believed to evoke hyperactivation of mTOR in muscles, leading to impaired insulin signaling (471). Furthermore, high levels of circulating BCAAs may exacerbate cardiac insulin resistance and myocardial contractile dysfunction through fostering mitochondria dysfunction and mTOR upregulation (474, 475).

3.2.1.2.3. Glucose. Current nutrition regimen consists of excessive carbohydrates from digestible polysaccharides to refined sugars which impose unfavorable health effects in human, a phenomenon commonly being referred to as "carbotoxicity" (476). Among various contributing factors for carbotoxicity, alteration in GLUT4, the insulin-responsive glucose transporter, serves as the major contributor for dampened glucose uptake in muscle and adipose tissues in obesity. Although loss of GLUT4 does not necessarily induce obesity, it drastically elevated serum glucose and insulin, decreased tissue glucose uptake, and imposed hypertension, reminiscent of noninsulin-dependent diabetes mellitus in human (477).

Other than GLUT4, sodium/glucose cotransporter 1 (SGLT1) functions as the main Na-dependent glucose cotransporter in heart (478). Cardiac SGLT1 (the main cardiac isoform) was shown to evoke an important role in acute IRI likely by way of facilitated glucose uptake, particularly in insulin resistance where GLUT4 regulation is compromised, although SGLT1 inhibition reduces obesity, incident diabetes, HF, and death (479, 480). In addition, SGLT6 [sodium-myoinositol cotransporter-1 (STIM1)] senses hyperglycemia and triggers the production of reactive oxygen species (ROS) in heart (481). SGLT2 is an emerging therapeutic target in the treatment of type 2 diabetes. However, SGLT2 is not expressed in the heart (478). Recent evidence suggested that SGLT2 inhibitors promoted energy expenditure, attenuated inflammation (polarizing M2 macrophages in WAT and liver) and insulin resistance in obesity, which may offer indirect cardiovascular protection (482).

In addition, mitsugumin 53 (MG53) is myokine/cardiokine secreted from hearts and skeletal muscle following high glucose or high insulin challenge to bind with the extracellular domain of the insulin receptor, thus allosterically inhibiting insulin signaling. Hyperglycemia is believed to be associated with elevated circulating MG53 in humans and rodents with diabetes mellitus (483).

3.2.2. Alternations of cardiac metabolism.

Alteration in fuel metabolism plays vital roles in both ATP-producing and non-ATP-producing energy homeostasis and pathogenesis of heart dysfunction in obesity. Cardiomyocytes switch main energy supply from carbohydrates to fatty acids during perinatal period, in concert with elevated mitochondrial oxidative phosphorylation and FAO (423). The heart maintains profound metabolic flexibility under stress such as nutrient excess, leading to changes in cardiac energetics and contractile function (135). For example, elevated LV wall stress in obesity evokes rises in myocardial oxygen consumption. The

rise in substrate supply in obese hearts triggers an increase in FAO in conjunction with suppressed glucose oxidation. Obesity promotes a switch in gene expression favoring FAO over glucose oxidation, which is initially adaptive although further dampens insulin sensitivity and metabolic flexibility over time, resulting in impaired cardiac efficiency and cardiac contractile anomalies (**FIGURE 5**). Regardless of precipitating factors, sustained metabolic derangements in obesity promote oxidative stress, inflammation, insulin resistance, lipotoxicity, and energy deprivation, all of which promote progression of HF (135).

3.2.2.1. LIPIDS. The fine interplay of uptake, metabolism and oxidation of fatty acids (FAs) is necessary to maintain ATP and lipid homeostasis and membrane biosynthesis in the heart. At the energy level, obesity cardiac dysfunction is characterized by elevated myocardial oxygen consumption, dampened cardiac efficiency, and overwhelmed oxidative stress, denoting a likely role for

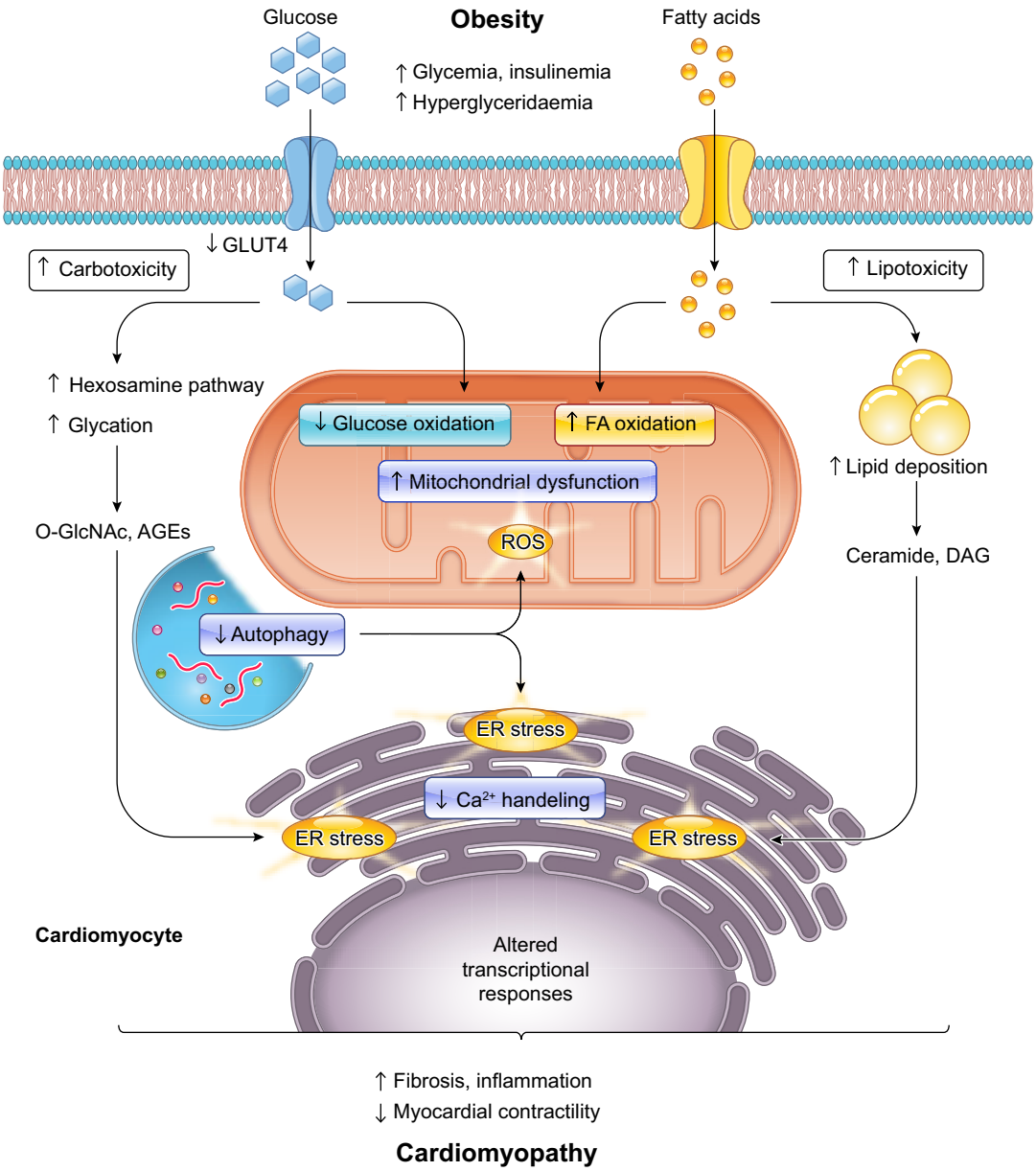


FIGURE 5. Metabolic stress and organelle dysfunction in obesity cardiomyopathy: Obesity leads to decreased myocardial glucose uptake and oxidation, increased fatty acid oxidation (FAO), and altered cardiomyocyte gene expression. Increased triglyceride accumulation and their products, such as ceramides and DAG, cause majority of lipotoxicity in hearts. Different metabolic pathways such as hexosamine and advanced glycation end-product (AGE) pathways have been identified as pro-oxidative processes and are usually elevated in uncorrected obesity. Autophagy activity in the heart declines with obesity, and its insufficiency is involved in the accumulation of reactive oxygen species (ROS) and the development of endoplasmic reticulum (ER) stress, leading to obesity-related cardiometabolic diseases. GLUT4, glucose transporter type 4; DAG, diacylglycerol; *O*-GlcNAc, β-linked *N*-acetylglucosamine; AGEs; advanced glycation end-products; FA, fatty acid; ROS, reactive oxygen species. Created with BioRender.com.

increased FAO in cardiac dysfunction. A multivariate, stepwise regression evaluation concluded that high BMI value was the sole independent determinant of higher myocardial oxygen consumption and lower LV efficiency (484). It is perceived that insulin resistance, evaluated using glucose area under the curve, functions as the independent predictor of elevated myocardial fatty acid uptake, utilization, and oxidation (484).

High FAO seems to be responsible for reduced oxygen efficiency and accumulation of fatty acid, derivatives that further compromises cardiac efficiency by uncoupling mitochondria (485). However, later studies suggested that the heart exhibits impaired capacity of FAO in the face of excess lipid supply in obesity, a notion that is supported by the beneficial effect of FAO stimulation on cardiac pathology. Given that malonyl CoA generation via acetyl CoA carboxylase 2 (ACC2) suppresses the entrance of long chain fatty acids into mitochondria, cardiac-specific knockout of ACC2 maintained FAO and, to our surprise, attenuated obesity-induced cardiac dysfunction (486). Shao and associates (487) suggested that elevated cardiac FAO protected against cardiomyopathy in chronically obese mice, in part, by preservation of mitochondrial function through parkin-mediated mitophagy. In addition, reduced cardiac efficiency noted in obesity should be attributed to mechanisms other than increased FAO, for instance, mitochondrial uncoupling and ROS (488).

An important hallmark of altered cardiac metabolism in obesity and other metabolic anomalies is the excess of substrate supply compared with demand for ATP synthesis. Even with elevated FAO, obese hearts are still filled with excess lipid accumulation prompting lipotoxic cardiomyopathy. Cardiac lipotoxicity denotes accumulation of excess fatty acids and associated triglyceride in parenchymal cardiomyocytes resulting cell death and cardiac anomalies (106, 353, 489, 490). Ultrastructural examination using electron microscopy has unveiled that obesity is associated with enlarged sarcoplasmic reticulum, disordered alignment of myofilaments, abnormal morphology of mitochondria, and numerous lipid droplets between myofibrils in cardiac tissues (491). Long-chain nonesterified fatty acids and their products, such as ceramides and diacylglycerols (DAGs), are mainly responsible for lipotoxic sequalae (492–494). Intramyocardial lipid overload was found to corelate with contractile dysfunction and alterations in gene expression in obese Zucker Diabetic Fatty (ZDF) rats, reminiscent of human failing hearts with lipid overload (495). It is conceived that presence of obesity-induced DAG accumulation in the heart signified the development of cardiac insulin resistance through PKCα-dependent inhibition of Akt, p70s6k activation, and IRS-1 Ser332/336 phosphorylation (496). Not surprisingly, pharmacological and genetic strategies targeting lipotoxicity yield salutary actions on the heart and overall metabolic health (381, 497, 498). For example, troglitazone therapy lowers obesity-induced myocardial TG and ceramide and prevents apoptosis and loss of cardiac function in obese ZDF rats (499).

Intramyocardial lipid deposition is often accompanied with upregulated nuclear receptors, peroxisome proliferator-activated receptor-α (PPARα)-regulated genes, myosin heavy chain-β, and proinflammatory cytokines including TNF-α. PPARα has long been known to govern fatty acid metabolism in the heart and mediate the development of lipotoxicity (490). PPARβ and PPARδ, on the other hand, participate in the homeostasis of both fatty acid and glucose metabolism. Given that PPARα generally governs genes involved in fatty acid metabolism, including uptake, storage and oxidation in the heart, emerging studies have tried to clarify how PPARα provokes the imbalance of lipid metabolism. It was recently demonstrated that fatty acids (FAs) upregulate glycogen synthase kinase-3α (GSK-3α) and thus phosphorylate PPARα at Ser280 in its ligand-binding domain, resulting in elevated transcription of a subset of PPARα targets and its biased activation, that is, only activation of its transcriptional activity of FA uptake and storage but not oxidation (500). The activator protein 1 members JunD and miR-494-3p may also play a role in lipid accumulation as levels of JunD and miR-494-3p were found dysregulated to correlate with myocardial TG content and echocardiographic indexes of LV dysfunction in obese human hearts (501).

3.2.2.2. GLUCOSE. In the setting of obesity, glucose uptake and oxidation are suppressed (135). Obesity-induced change in insulin signaling directly impedes insulin-stimulated GLUT4 translocation and glucose uptake. Restoring glucose oxidation is believed to improve obesity-induced cardiac injury. PPARα activation could increase glucose oxidation in the heart and alleviate contractile dysfunction in obesity (502). However, profound rises in intracellular glucose and sustained stimulation of glucose uptake and oxidation remodeled the cardiac metabolic network and dampened metabolic flexibility. In this context of high-glucose stimulus, high-fat diet-induced FAO is obtuse, leading to overwhelmed oxidative stress and cardiac dysfunction (503).

As a result of insulin resistance and elevated FAO, obesity is associated with dampened glucose uptake and utilization for ATP synthesis, albeit with possibly elevated accessary glucose metabolism flux (135). For example, nutrient excess in obesity may promote hexosamine biosynthetic pathway resulting in protein posttranslational modification by *O*-GlcNAc transferase (OGT)-mediated *O*-linked β-*N*-acetylglucosamine (*O*-GlcNAc) moieties. Overexpression of adipose OGT suppresses lipolysis and

exacerbates diet-induced obesity (504). AMPK, on the other hand, inhibits *O*-GlcNAcylation through regulation of glutamine:fructose-6-phosphate aminotransferase (GFAT) phosphorylation to alleviate *O*-GlcNAcylation of target proteins such as troponin T. Blockade of *O*-GlcNAcylation using inhibitors of the GFAT mitigates cardiomyocyte hypertrophy (505).

3.2.2.3. OTHER SUBSTRATES. In pathological cardiac hypertrophy and HF, the ATP-generating modality is altered to promote energy production from glycolysis, anaplerosis, lactate, BCAAs, and ketone bodies (506). However, glycolysis and utilization of lactate, BCAAs, and ketone bodies cannot adequately compensate for loss of glucose oxidation in obesity, thus prompting energy deficit and onset of HF (423). Chronic loss of insulin sensitivity imposes blunted BCAA oxidation in the liver and adipose tissues, resulting in increased workload of BCAA oxidation in muscles (507). In addition, BCAA oxidation is vital for cardiac function. Suppression of the essential step for BCAA oxidation namely branched-chain α-keto acid dehydrogenase (BCKDH) (with BCATm being the rate-limiting enzyme for BCAA oxidation) reduces cardiac systolic function in mice whereas 3,6-dichlorobenzo[b]thiophene-2-carboxylic acid, a pharmacological inhibitor of BCKDH kinase, to lower plasma BCAAs, enhances cardiac BCAA degradation and thus preserves heart contractility (474).

3.2.3. Mitochondrial dysfunction.

Mitochondrial dysfunction, including the inability to generate ATP, disturbed mitochondrial dynamics, insufficient mitophagy, and accumulation of reactive oxygen species (ROS), plays a rather unique role in the onset of cardiomyopathy in obesity (105, 508–511). First, evidence was obtained that the inability of the mitochondria in obese heart to appropriately utilize glucose and the consequent switch from glucose to FAO results in metabolic inflexibility (485) (**FIGURE 5**). As the reliance on FAO requires a greater oxygen consumption and free fat acids (FFAs) instinctively causes mitochondrial uncoupling, these changes pose a significant threat to cardiovascular health through reduced ATP generation, decreased cardiac efficiency, and as a consequence, defects in contractile function (512, 513).

Over the past decades, many advances have been achieved toward understanding mitochondrial biogenesis, dynamics, quality control and their involvement in the progression of obesity-related cardiomyocyte dysfunction. Mitochondrial proliferation was increased in db/db hearts (514). Morphological transition from mitochondria network to fragmented mitochondria was noted in obese cardiomyocytes (515). Palmitate challenge in neonatal rat cardiomyocytes initially turned on mitochondrial respiration, along with increased mitochondrial polarization and ATP production, while sustained incubation of palmitate (>8 h) evoked ROS production and mitochondrial fission (516). Lipid overload-induced cardiomyocyte apoptosis and cardiac dysfunction were likely due to altered posttranslational modifications of the mitochondrial fission and fusion proteins, including increased ubiquitination of A-kinase anchor protein 121 (AKAP121), dynamin-related protein 1 (Drp-1), and proteolytic processing of optic atrophy 1 (OPA1) (515, 516).

Dysfunctional mitochondria are removed by a specialized form of autophagy, referred to as mitophagy. Imbalanced mitochondrial biogenesis and mitophagy also occurs in the development of metabolic cardiomyopathy. Mitophagy is induced by high-fat-diet consumption, while deficiency in mitophagy aggravates high-fat intake-induced cardiomyopathy (517, 518). Mitochondria and endoplasmic reticulum (ER) are interconnected organelles, numerous proteins were proposed to tether the two organelles together at specific sites, referred to as mitochondria-associated ER membranes (MAMs) (519). Interestingly, despite that disruption of MAMs instigates aberrant Ca^{2+} signaling and cardiac anomalies, a recent study suggested that high-glucose-induced FUNDC1-mediated MAMs formation and mitochondrial calcium overload in the cardiomyocytes, leading to functional cardiac abnormalities (519, 520).

3.3. Endoplasmic Reticulum Stress

The endoplasmic reticulum (ER) is most essential for Ca^{2+} storage, lipid biosynthesis, and protein sorting and processing. A wide variety of gene products pass through the ER lumen, governing both physiological and pathophysiological processes (521, 522). Cellular perturbations in obesity interrupt ER homeostasis, resulting in the buildup of unfolded/misfolded proteins and pronounced ER stress (523, 524). To sustain ER homeostasis, cells utilize protein quality-control systems through unfolded protein response (UPR), endoplasmic reticulum associated degradation (ERAD), and autophagy (525) (**FIGURE 6**). The ER-resident proteins are predominantly removed by ERAD for proteasomal degradation inside ER, while protein aggregates within the ER lumen may be destroyed through autophagy degradation (524, 525). When misfolded proteins accumulate in ER, UPR can be triggered by activation of three main UPR sensors, inositol-requiring enzyme 1α, protein kinase R-like endoplasmic reticulum kinase (PERK), and activating transcription factor 6, on ER membrane, to cope with unfolded and misfolded proteins (521). When the UPR is unable to handle unfolded and/or misfolded proteins in the ER, the ER-initiated apoptotic signaling is turned on (523).

SR/ER and ER stress in obesity are also closely related to obesity in the heart (524). Levels of PERK were suppressed in the liver and heart, following 16 and 8 wk, respectively, following high-fat diet intake (526). High-fat diet intake upregulated levels of GRP94 and CHOP in left ventricles (LV) from 5-mo-old Lee-Sung pigs (527). Palmitate increased ER stress in H9C2 cells, manifested as levels of p-PERK, p-eIF2α, and transmission electron microscopy examination (528). Furthermore, palmitate-triggered ER stress induced adiponectin resistance through AMPK phosphorylation and reduced APPL1 levels (528). Chronic ER chaperone tauroursodeoxycholic acid treatment rescued against increased systolic blood pressure, glucose intolerance, cardiac hypertrophy, and cardiac contractile dysfunction in obese mice through reconciliation of obesity-associated drop in sarco(endo) plasmic reticulum Ca^{2+}-ATPase (SERCA) function, rises in serine phosphorylation of IRS, total and phosphorylated cJun, as well as ER stress markers Bip, peIF2α, and pPERK (77).

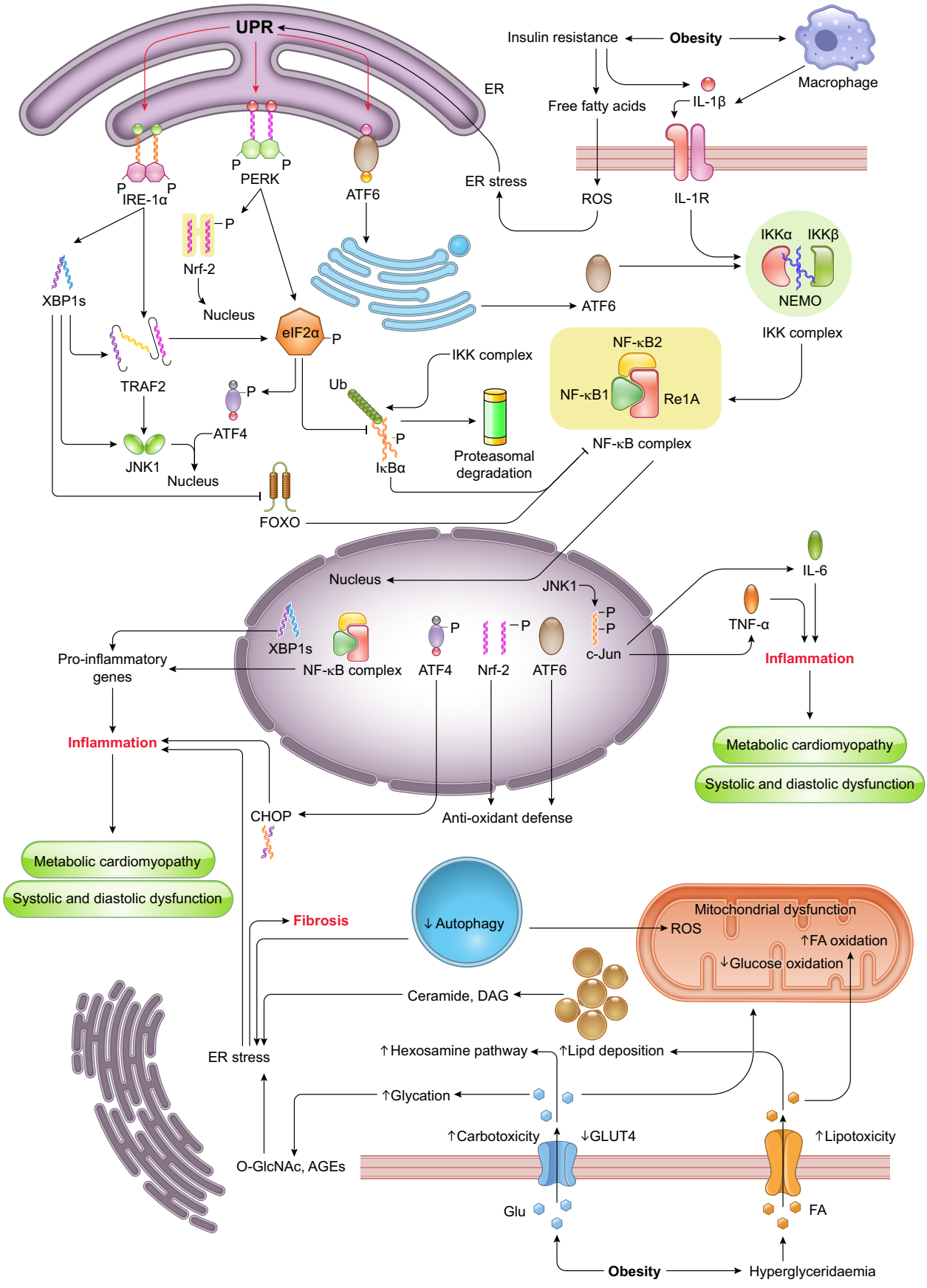
3.4. Calcium Handling

Ample vital mitochondrial function including ATP production and mitochondrial metabolism are heavily controlled by Ca^{2+} signal, an essential intracellular second messenger that reaches the mitochondrial intermembrane space and then mitochondrial matrix, to participate in the regulation of proteins, enzymes and transporters (e.g., AMPK, pyruvate dehydrogenase kinase 4, pyruvate dehydrogenase phosphorylation, and GLUT4) required for ATP synthesis and mitochondrial metabolism (529). Intracellular and mitochondrial Ca^{2+} is tightly regulated in a narrow range to preserve the overall cellular Ca^{2+} homeostasis and cardiomyocyte contractility and defective Ca^{2+} handling (both intracellular and mitochondrial) is supposed to play a major role in obesity-related cardiac dysfunctions noted as prolonged diastolic relaxation, decreased fractional shortening, and compromised ejection fraction (530–533). Besides, extracardiac findings have suggested other potential mechanisms underlying calcium overload and energy metabolism. For instance, elevated intracellular Ca^{2+} in hepatocytes during obesity inhibits insulin-stimulated Akt phosphorylation and its key downstream signaling molecules by inhibiting membrane localization of pleckstrin homology domains (534). Obesity-induced increase in PDK4 activity augments MAM formation to promote Ca^{2+} transfer from SR/ER to mitochondria and suppresses insulin signaling in skeletal muscle (535).

3.4.1. Calcium handling in sarcoplasmic reticulum.

During the process of excitation-contraction coupling in cardiomyocytes, activation of voltage-gated L-type Ca^{2+} channels evokes Ca^{2+} releases from sarcoplasmic reticulum (SR) via ryanodine receptors (RyRs), a process commonly known as Ca^{2+}-induced Ca^{2+} release. Cardiac relaxation is driven by Ca^{2+} reuptakes via SR Ca^{2+}-ATPase (SERCA) and Ca^{2+} extrusion from sarcolemma Na^{+} and Ca^{2+} exchanger. Dephosphorylated phospholamban at Thr17 and Ser16 inhibits SERCA2a and suppresses Ca^{2+} uptake (536). Animal studies have reported prolonged Ca^{2+} clearance including reduced intracellular Ca^{2+} amplitude and decay in obese hearts, coinciding with prolonged relaxation (537–540). Increased SR Ca^{2+} leak via RyR2 plays a critical role in the progression of HF and cardiac arrhythmia. Suppressed SERCA2a activity is known to contribute to impaired relaxation and Ca^{2+} handling in ob/ob mice and sucrose-fed rats (538). However, reduced SERCA2a activity may result from SERCA oxidation in ob/ob mice, while SERCA2a dysfunction was associated with inhibited phosphorylation of phospholamban at Ser16 and Thr17 in sucrose-fed rats. More evidence has indicated unaltered expression of SERCA2a and phospholamban (or phosphorylation) in obese hearts, indicating possible involvement of posttranslational modification of SERCA2a (539). Results from studies in animal models with HF suggested that inhibition of SERCA2a activity is associated with the sulfonylation at Cys674 and nitration at Tyr294/295 (541). Downregulation of SIRT1, a class III histone deacetylase, increased SERCA2a acetylation at Lysine 492, leading to reduced SERCA2a activity and cardiac defects (542, 543). Moreover, myocardial dysfunction was correlated with impaired L-type Ca^{2+} channel activity in the absence of altered SERCA2a function and L-type Ca^{2+} channel protein levels in high-fat-fed rats (544). Among various mechanisms proposed for altered Ca^{2+} regulation in obesity, stromal interaction molecule 1 (STIM1) is believed to regulate cardiac Ca^{2+} signaling by sensing reduced SR Ca^{2+} level and interact with plasma membrane Orai channels to induce Ca^{2+} influx, leading to prolonged action potential duration and cardiac hypertrophy (545). SMIT1 overexpression exacerbated glucotoxicity and sensitized cardiomyocytes to hyperglycemia (481). Nonetheless, further study is needed to discern if this mechanism prevails in obesity cardiomyopathy.

Cardiac systolic dysfunction in various obese animals is mainly characterized by slightly decreases in the amplitude and decay rate of cardiomyocyte shortening, which may attribute to the decreased amplitude of Ca^{2+} transients (104, 537, 538, 546, 547). It was observed that diminished cardiac function in the fat-fed dogs was associated with the reduced RyR2 activity, which is not due to changes of protein expression but the increased phosphorylation of RyR2 (548). However, the results from the obese Zucker rats exhibited cardiomyocyte dysfunction, which was related to the decreased expression of L-type Ca^{2+} channel and eventually contributed


UPR
ER
IRE-1α
PERK
ATF6
ER stress
Insulin resistance
Obesity
Macrophage
Free fatty acids
IL-1β
ROS
IL-1R
Nrf-2
Nucleus
XBP1s
eIF2α
TRAF2
ATF4
JNK1
Nucleus
FOXO
ATF6
IKKα
IKKβ
NEMO
IKK complex
NF-κB2
NF-κB1
Re1A
NF-κB complex
IKK complex
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IκBα
Proteasomal degradation
Nucleus
JNK1
XBP1s
NF-κB complex
ATF4
Nrf-2
ATF6
c-Jun
IL-6
TNF-α
Inflammation
Pro-inflammatory genes
Inflammation
Metabolic cardiomyopathy
Systolic and diastolic dysfunction
CHOP
Anti-oxidant defense
Metabolic cardiomyopathy
Systolic and diastolic dysfunction
Fibrosis
↓Autophagy
Mitochondrial dysfunction
ROS
↑FA oxidation
↓Glucose oxidation
Ceramide, DAG
ER stress
↑Hexosamine pathway
↑Lipid deposition
↑Glycation
↑Carbotoxicity
↓GLUT4
↑Lipotoxicity
O-GlcNAc, AGEs
Glu
FA
Obesity
Hyperglyceridaemia

to the prolonged duration of AP (549). Additionally, it has been suggested that the posttranslational modifications, including S-glutathionylation, *S*-nitrosylation, and disulfide oxidation could regulate the activity and function of RyR2 in HF (550). Further research needs to establish whether these PTM of RyR2 participate in the cardiac dysfunction of obesity.

3.4.2. Ca^{2+} overload and mitochondria.

Mitochondrial Ca^{2+} homeostasis is regulated by various organelles. The ER can release Ca^{2+} into the mitochondria quickly through Ca^{2+} channels in the MAM area to maintain Ca^{2+} homeostasis of mitochondria in physiological settings (551). There are a variety of Ca^{2+}-regulated transporters in the MAM region, including inositol 1,4,5-trisphosphate receptor (IP_3R) and ryanodine receptors (RyRs) located on the ER and voltage-dependent anion channel 1 (VDAC1) and mitochondrial Ca^{2+} uniporter (MCU) located on the mitochondrial membrane (551). One of the most important Ca^{2+} transport complexes between ER and mitochondria is formed by VDAC1 and IP_3R, which are bridged together by Grp75 (551). Both increased MAM formation or the MAM Ca^{2+} channel hyperactivation would result in mitochondria uptake of excessive Ca^{2+} in stress condition, prompting mitochondrial Ca^{2+} overload, mitochondrial permeability transition pore (mPTP) opening, mitochondrial dysfunction, and ultimately cell death (551).

Appropriate Ca^{2+} handling is essential to mitochondria, where Ca^{2+} uptake supports oxidative phosphorylation (OXPHOS) and ATP production to limit excessive ROS production during cardiac contraction. ROS production is significantly increased in cardiomyocytes from obese animals (552, 553), and these rises correlate with prolonged relaxation in the heart (546, 554). Data from our group revealed that loss of mitochondrial autophagy receptor FUNDC1 accentuated high-fat diet-induced cardiac remodeling, functional and mitochondrial anomalies likely through rises in type 3 IP_3R and mitochondrial Ca^{2+} overload (555). Recent evidence revealed a role for diastolic SR Ca^{2+} leak via RyR2 and type 2 IP_3R (IP_3R2) in mitochondrial Ca^{2+} overload, ROS production and cardiac dysfunction (537, 556). Furthermore, electrically evoked Ca^{2+} transients were smaller and slower, associated with the increased IP_3 level in *ob/ob* cardiomyocytes (557). In addition, it was suggested that ROS production was associated with increased carbonyl oxidation of SERCA2a and abnormal relaxation in *ob/ob* mice (538). Moreover, overexpression of mitochondrial Na^+/Ca^{2+} exchanger (NCLX), the primary mitochondrial Ca^{2+} extrusion machinery in cardiomyocytes, plays a protective effect in the clearance of mitochondrial Ca^{2+} overload, alleviating cardiomyocyte necrosis and HF (558), although its role in obesity cardiomyopathy remains unclear.

Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII) is a multifunctional serine/threonine kinase to mediate various physiological responses upon β-adrenergic activation (559). CaMKII is upregulated and mediates Ca^{2+} handling in various cardiac diseases including obesity-related cardiomyopathy through phosphorylating and regulating RyR, IP_3R2, and phospholamban (559). Activation of CaMKII is suspected to provoke mitochondrial dysfunction, oxidative stress, ER stress, inflammation, and cell apoptosis in palmitate-induced cell hypertrophy and fibrosis in H9C2 cells (560). Sustained CaMKII activation interrupts intracellular Ca^{2+} homeostasis. For instance, CaMKII phosphorylates RyR to affect its open probability and promotes arrhythmogenic spontaneous SR Ca^{2+} release in heart diseases (559). In addition, CaMKII may facilitate mitochondrial Ca^{2+} entry through upregulation of MCU conductance, resulting in mitochondrial Ca^{2+} overload, mPTP opening and dissipation of mitochondrial inner membrane potential (561). In this context, CaMKII links ER stress and mitochondrial dysfunction through Ca^{2+} transfer between ER and mitochondria.

3.5. *Autophagy*

Autophagy is an evolutionarily conserved process to engulf cytoplasmic cargos and organelles through autophagosomes, fusion with lysosomes to form autophagolysosomes for production of ATP and macromolecules. Autophagy serves as a double-edged sword with

FIGURE 6. Obesity-mediated endoplasmic reticulum (ER) stress underlies cardiometabolic disorders: Obesity induces certain conditions such as hyperglyceridemia, glycemia, insulin resistance, and macrophage activation, all of which, in turn switches on several pathways culminating in ER stress, inflammation, and ultimately cardiometabolic disorders. Insulin resistance induces ER stress, which activates three branches of unfolded protein response (UPR) including ATF6, PERK, and IRE-1α. IRE-1α/TRAF2/JNK1/c-Jun pathway induces inflammation via TNF-α and IL-6, while PERK/eIF2α/IκBα pathway and ATF6 trigger NF-κB complex-mediated inflammation. Macrophage also produces IL-1β, which activates IKK and NF-κB complexes leading to inflammation. Hyperglyceridemia and glycemia induce carbotoxicity and lipotoxicity, which instigates metabolic alterations resulting in ER stress and inflammation. IRE-1α, inositol-requiring protein-1; PERK, protein kinase RNA-like ER kinase; ATF6, activating transcription factor-6; IKK, I-κb-kinase; NF-κB, nuclear factorκB; IκBα, I-κb-α; Ub, ubiquitin; eIF2α, eukaryotic initiation factor 2α; Nrf-2, nuclear factor-E2-related factor; XBP1s, X-box-binding-protein-1 spliced; TRAF2, TNF receptor-associated factor 2; JNK1, C-Jun NH_2-terminal kinase 1; ATF4, activating transcription factor-4; FOXO, forkhead box O; c-Jun, a transcription factor; CHOP, C/EBP homologous protein; FA, fatty acid; Glu, glucose; GLUT4, glucose transporter type 4; DAG, diacylglycerol; *O*-GlcNAc, β-linked *N*-acetylglucosamine; AGEs, advanced glycation end-products.

physiological levels of autophagy being cytoprotective whereas unchecked or excessive autophagy being self-destructive for cannibalistic cell death - a form of nonapoptotic cell death or "type II programmed cell death." Three types of autophagy are identified modality of autophagosome delivery into lysosomes: microautophagy, macroautophagy and chaperone-mediated autophagy (133, 562, 563).

Autophagy levels alter in response to variations in nutrient status such as fat/caloric intake and may unfavorably affect local (such as in a metabolically active organ) or global metabolism to promote metabolic derangement. Both elevated and suppressed autophagy have been noted in metabolic disorders including obesity (547, 564–567), due to an interplay among genetic factors, environment and energy imbalance. Three major risks factors in obesity, dyslipidemia, hypertension and insulin resistance/hyperglycemia are believed to be responsible for disturbed autophagy response in obesity. Meanwhile, deranged autophagy, in particular loss of autophagy, fosters metabolic derangement, insulin resistance and obesogenesis (133). In addition, considering the essential role for autophagy in the regulation of cardiac homeostasis, one should not neglect the direct contribution of autophagy derangement in cardiac proteotoxic pathology (aka, cardiac proteinopathy), and development of cardiomyopathies (568–575). Ample evidence has depicted that activation of autophagy through autophagy inducers or the master regulator of lysosomal function transcription factor EB (TFEB) effectively rescues cardiac protein quality control, cardiac remodeling and contractile function under various pathological settings (568, 570, 571, 576).

3.5.1. Cardiac autophagy in obesity.

Autophagy defects are closely associated with adiposity. For example, mice with global or tissue-specific (e.g., liver and pancreas) ablation of autophagy associated proteins including Atg7, Becn2, Bif, LAMP2, and Tfeb present obesogenic phenotypes or are predisposed to diet-induced or genetic adiposity (133). Autophagy also governs pathological sequalae of obesity, mainly through buildup of autophagy substrates including protein aggregates, lipid droplets, and damaged mitochondria (563, 577).

While the molecular mechanisms of autophagy have been extensively examined in obesity, how obesity-related autophagy changes in cardiomyocytes remains unclarified. Although research has shown that autophagosomes are normally formed in obesity, autophagy flux is disrupted because of defects in lysosome and impaired fusion of autophagosomes and lysosomes to preclude autophagic degradation (578, 579). Lack of an additional accumulation of LC3-II and p62 in chloroquine-treated high-fat-fed hearts favored the notion that elevated autophagosomes may be secondary to compromised autophagosome turnover (565). Impaired autophagy flux contributes to the development of cardiac dysfunction caused by obesity (580, 581), while the underlying mechanisms remain unclear. For instance, both genetic and diet-induced models of obesity noted a drastic loss in cardiac autophagy in concordant with downregulated unc-51 like kinase-1 (ULK1) (582). Of note, cardiomyocyte-specific knockout of Ulk1 disrupts autophagy and mimics the increase in cardiac lipoprotein lipase (LPL) levels occurred in obesity models. In the heart, LPL prompts myocardial fatty acid buildup via intravascular triglyceride (TG) hydrolysis. Concurrent ablation of LPL and ULK1 mitigated high-fat intake-evoked aberration in triglyceride (TG), diacylglycerol, and cardiac function, indicating a protective role of ULK1-mediated autophagy in obesity-induced cardiomyopathy through the regulation of lipid metabolism (582).

It was noted that although autophagic flux is transiently activated by high-fat diet consumption, peaking at 6 wk, it is ultimately attenuated (518, 580, 581). However, mitophagy, evaluated with Mito-Keima, continues to increase even after 2-mo high-fat-diet feeding (518). Deletion of Parkin partially impaired mitophagy, increased lipid accumulation, and exacerbated cardiac dysfunction during high-fat-diet feeding (518). These findings denote an essential role of mitophagy in cardiac protection against high-fat uptake.

3.5.2. Lipophagy in the heart during obesity.

Lipid storage can be evaluated using lipophagy, a specific subset of selective autophagy that targets lipid droplets and catabolizes their components into FFAs and glycerol (583). Altered cardiac lipophagy has been solidified in murine obese models, denoting a role for lipophagy in high myocardial lipid accumulation (584). Transmission electron microscopy can be employed to monitor the size and quantity of lipid droplets, along with lipid droplet-associated double-membrane structures, corresponding to autophagosomes (583). Consistent with the changes of macroautophagy in the heart during obesity, data from both immunoblotting and electron microscopy revealed more lipid droplets and autophagosomes with fewer autolysosomes in the hearts of high-fat diet-fed mice, denoting inhibition of autophagosome degradation (584). Among various possible scenarios, compromised ability of FGF21 to promote autophagy/lipophagy was shown to exacerbate lipid accumulation and structural derangements in obese murine hearts (381).

3.5.3. Autophagy stimulation and cardioprotective effects.

Obesity-related cardiac anomalies are associated with the disruptions of signaling pathways involved in cardiomyocyte autophagy, while activation of autophagy/mitophagy retards cardiac dysfunction in obesity (487, 547, 580). Injection of Tat-Beclin1 effectively inhibits lipid accumulation and protects against cardiac dysfunction by restoring autophagy or mitophagy (518, 582). SGLT2 inhibitors induce a transcriptional paradigm that mimics nutrient, and oxygen deprivation and activates autophagy, thereby mitigating cardiomyocyte dysfunction (585). Overexpression of ALDH2 increased Beclin-1, Atg7, and AMPK as well as decreased mTOR have been shown to lead to autophagy induction and alleviated palmitic acid-induced cardiac dysfunction via autophagy regulation in a SUV39H-Sirt1-PGC-1α deacetylation-dependent manner (586).

4. THERAPEUTIC IMPLICATIONS OF OBESITY CARDIOMYOPATHY

4.1. Management of Obesity

Long-term pharmacotherapy of obesity is structured on reduction of energy intake, facilitation of satiety, lowering sensation of hunger, and caloric absorption, along with lifestyle modification intervention (587). In severe or morbid obesity, intragastric balloon insertion, shock therapies, and bariatric surgery can be applied (587–589). Nonetheless, effective antiobesity therapy has been greatly hindered by the lack of a better understanding of the precise interplay between genetic and nongenetic factors (e.g., nutrition and environmental cues) in the etiology of obesity and obesity complications.

4.1.1. Cornerstone: weight loss.

Despite the debatable benefits of obesity paradox (590), constellation of findings suggested weight loss, in particular by way of cardiorespiratory fitness and regular exercise, plays an indispensable role in the prevention and management of CVD in obese individuals (591). Obesity-related cardiac remodeling and dysfunction is prevented or even be reversed with purposeful weight loss (591, 592). For example, a switch from high-fat to low-fat diet in obese mice with heart failure drastically lowered the body weight gain, retarded cardiac remodeling, as well as improved cardiac insulin sensitivity and diastolic function (593), denoting a beneficial effect of weight loss. This is echoed by the ample beneficial responses on cardiac geometry and function in overweight and obese individuals with bariatric surgery or lesser levels of weight loss using caloric restriction (CR) (**TABLE 2**). Furthermore, a retrospective study found that weigh loss between annual physical examinations displayed beneficial effects in general populations (616). Nonetheless, coexisting chronic diseases and the duration and severity of overweight and physical limitations should be considered to assess the health risks and benefits of treatment options. Efficient strategies with evidence-based support to improve health and quality of life mainly include lifestyle intervention, pharmacotherapy, and bariatric surgery (591).

4.1.2. Lifestyle intervention.

Lifestyle interventions are geared to modify dietary habits and physical activity. Given their low cost, great convenience, improvement in the quality of life and the minimal risk of complications, lifestyle interventions are often recommended as the first option for obesity management. Of 130 severely obese participants randomized, one-year intensive lifestyle intervention resulted in a reduction of ~10 kg in weight and favorable changes in CVD risk factors (617). Weight regain is a common situation whenever a lifestyle intervention program is failing to produce additional weight loss and patients tend to be reluctant to maintain the long-term behavioral modification. Interestingly, a 20-yr follow-up study found that a better adherence to healthy dietary patterns weakens the genetic association with weight gain (618). Individuals at high genetic risk for obesity were proposed to receive greater benefits from improved diet quality (618). Physical inactivity is closely associated with chronic subclinical myocardial damage, while physical activity is suggested to attenuate obesity-associated cardiac remodeling (619). The salutatory impact of habitual physical activity is partially obtained from its effects on traditional cardiovascular risk factors. At the cellular level, regular physical activity contributes to maintain vascular homeostasis and to reduce systemic and cardiac inflammation (620, 621).

Although excessive CR has generated some debatable or even detrimental outcomes on cardiac geometry and contractile function (622–624), emerging studies have highlighted the potential benefits of CR on obesity-associated heart diseases (622). Thirty-four obese although otherwise healthy subjects consumed a very low-calorie diet for 6 wk. Consumption of very low-calorie diet decreased weight, myocardial fatty acid uptake, triglyceride content, mass and cardiac work. Although global insulin sensitivity was improved one-third, with insulin-stimulated myocardial glucose uptake remained unchanged (598). The INFINITE study involving 180 older (65–79 yr) obese men and women examined the

Table 2. ***Effects of weight loss on cardiac function and morphology in human subjects***

Authors (Year) (Ref. No.)	Sample Size	Intervention and Follow-Ip	Baseline BMI	BMI after Weight Loss	Cardiac Function after Weight Loss	Cardiac Structure after Weight Loss
Naylor et al. (2008) (594)	23	Resistance training, 8 wk	32.5 ± 1.9	30.2 ± 2.6	Improved early diastolic myocardial velocities	No change in LV geometry
Amaro-Gahete et al. (2021) (595)	12	Physical exercise training, 12 wk	32.1 ± 3.6	31.4 ± 2.7	Increased LV end diastolic diameter	Not assessed
Serrano-Ferrer et al. (2014) (596)	39	Lifestyle intervention (diet and exercise), 3 mo	31.9 ± 3.5	28.8 ± 3.2	Improved RV global longitudinal strain and early diastolic strain rate; No change in TDI indices	Not assessed
Haufe et al. (2012) (597)	170	Hypocaloric diets, 6 mo	32.9 ± 4.4	30.4 ± 4.3 (reduced carbohydrate), 30.6 ± 3.9 (reduced fat)	No change in LV function	Lower LV mass
Viljanen et al. (2009) (598)	34	Hypocaloric diet, 6 wk	33.7 ± 0.7	29.9 ± 0.7	Improved cardiac output, decreased blood pressure	Lower LV mass
Karimian et al. (2017) (599)	32	Hypocaloric diet, 6 wk	40.3 ± 6.6	33.2 ± 6.1	Reduced blood pressure and partially normalized diastolic dysfunction	Not assessed
Varli et al. (2010) (600)	13	Hypocaloric diet plus orlistat, 6 mo	39.9 ± 4.3	36.1 ± 4.6	Improved LV diastolic function	Lower LV mass
Gulsin et al. (2020) (601)	87	Hypocaloric diet or aerobic training, 12 wk	36.6 ± 5.5	34.5 (routine care), 33.0 (exercise), 30.3 (low-energy diet)	No change in LV diastolic function	Less concentric LV remodeling and aortic stiffness
Andersson et al. (2016) (602)	68	Dietary intervention, 2 yr	32.6 ± 0.6	31.0 (Nordic nutrition recommend diet), 29.4 (Paleolithic-type diet)	Improved cardiac function	Lower LV mass
de las Fuentes et al. (2009) (603)	60	Dietary intervention, 2 yr	37 ± 3	4.1 ± 8.8 kg loss in weight	No change in LV diastolic and systolic function	Lower LV mass
Leung et al. (2016) (604)	8	Bariatric surgery, 9 mo	44 ± 9	35 ± 6	Improved LV global longitudinal strain and LV EF	Not assessed
Giudici et al. (2020) (215)	26	Bariatric surgery, 8 mo	47.9 ± 7.1	33.4 ± 6.9	Reduced carotid arterial stiffness and improved LV diastolic function	No change in LV geometry or mass
Kaier et al. (2014) (605)	52	Bariatric surgery, 6 mo	42.4 ± 4.6	31.5 ± 2.6	Improved RV and LV global strain, EF	Lower LV mass
Garza et al. (2010) (606)	57	Bariatric surgery, 3.6 yr	49 ± 9	35 ± 8	No change in LV function, RV function or EF	Reduced cardiac remodeling
Ikonomidis et al. (2007) (607)	60	Bariatric surgery, 3 yr	48.7 ± 7.8	23 ± 1	Improved LV diastolic and aortic function	Reduced LV hypertrophy

Continued

Table 2.—*Continued*

Authors (Year) (Ref. No.)	Sample Size	Intervention and Follow-Ip	Baseline BMI	BMI after Weight Loss	Cardiac Function after Weight Loss	Cardiac Structure after Weight Loss
Hsuan et al. (2010) (608)	66	Bariatric surgery, 3 mo	43.3 ± 6.3	34.1 ± 5.6	Improved peak systolic mitral annular velocity and diastolic indices	Lower LV size, relative wall thickness, LV mass index; no change in chamber size
Algahim et al. (2010) (609)	15	Bariatric surgery, 2 yr	46.7 ± 1.7	32.4	Not assessed	Decreased LV mass
Owen et al. (2011) (300)	423	Bariatric surgery, 2 yr	47.9 ± 7.0	32.2 ± 7.8	Improved LV and RV function	Decreased cardiac remodeling
Jhaveri et al. (2009) (610)	17	Bariatric surgery, 17 mo	44.1 ± 4.2	29.9 ± 4.7	No change in LVEDV, RVEDV, or EF	Decreased LV and RV mass
Lin et al. (2011) (611)	30	Bariatric surgery, 16 mo; Diet, 8 mo	39 ± 6	36 ± 7 (diet), 29 ± 5 (bariatric surgery)	Improved LV diastolic function	Lower LV mass
Valezi and Machado (2011) (612)	43	Bariatric surgery, 1 yr	41.8 ± 4.4	28.4 ± 3.8	Increased EF, improved diastolic function	Lower LV mass, interventricular septum, posterior wall thickness
Luaces et al. (2012) (613)	41	Bariatric surgery, 1 yr	47.41	30.43	Decreased early mitral velocity, increased mitral inflow E/A ratio	Decreased cardiac remodeling
Rider et al. (2009) (614)	30	Bariatric surgery or diet, 1 yr	39.7 ± 7.6	32.2 ± 5.3	Improved LV diastolic function	Decreased LV and RV mass
Alpert et al. (2015) (615)	67	After bariatric surgery	46.3 ± 5.2	34.5 ± 5.7	Reduced QT interval	Decreased LV mass normalized to height

E/a ratio, early-to-atrial wave ratio; EF, ejection fraction; LV, left ventricle; LVEDV/RVEDV, left/right ventricular end-diastolic volume; RV, right ventricle; TDI, Tissue doppler imaging.

effects of combined aerobic exercise with CR. The investigators noted that combination of aerobic exercise with even moderate CR (−250 kcal/day) seems to be more efficacious for cardiorespiratory fitness, fatigue and disability, and glucose control compared with exercise alone (suggested to be as effective as higher-dose CR −250 kcal/day) (625). Therefore, implementing CR with an aerobic exercise program would greatly potentiate the benefits on the heart.

4.1.3. Pharmacotherapy.

4.1.3.1. FOOD AND DRUG ADMINISTRATION-APPROVED MEDICATIONS FOR WEIGHT LOSS. Drug therapy in combination with lifestyle modification, produce beneficial effects on weight control and various obesity complications, particularly CVDs (589, 626). Development and approval of antiobesity drugs, however, have been challenging due to the adverse effects (cardiac arrhythmia, cataracts and neurotoxicity) of earlier weight loss medications such as 2,4,-dinitrophernol and fenfluramine. The food and drug administration (FDA) criteria for approval of antiobesity drugs have been stringent ever since the release of standard guideline in mid-1990s. A drug must elicit a significant placebo-adjusted weight loss of >5% in 1 yr or over 35% patients should reach >5% weight loss, in addition to overt improvement of metabolic biomarkers including blood pressure, blood lipid and glucose levels (627). Up-to-date, five drugs have been approved by FDA (three monotherapies: orlistat, lorcaserin, liraglutide and two combined therapies: phentermine/topiramate, naltrexone/bupropion) for obesity. The European Medicines Agency (EMA) has approved only three drug therapies (orlistat, bupropion/naltrexone, and liraglutide). All these medications yield a placebo-adjusted weight loss of >5% over a year. Among which, phentermine-topiramate and liraglutide display the highest efficacy of >5% weight loss whereas

liraglutide and naltrexone-bupropion exhibit the lowest rate of discontinuation of medication due to appearance of adverse events (628–631).

Orlistat, a selective pancreatic lipase inhibitor to alleviate intestinal digestion and absorption of fat, is approved by both FDA and EMA to induce weight loss in conjunction with caloric restriction. Orlistat is also indicated to reduce the risk of T2D and dyslipidemia, independent of its weight loss efficacy (627). Orlistat needs to be taken with meals and is indicated for patients with a BMI >30 or >28 when other risk factors (e.g., hypertension, diabetes, and hyperlipidemia) are present. Pooled data from randomized clinical trials suggested beneficial effects of orlistat in glucose tolerance and T2D development in obese individuals with impaired fasting glucose.

Lorcaserin, a hypothalamic 5-HT2C receptor agonist that acts on anorexigenic POMC neurons in the hypothalamus, is an appetite suppressant approved by the FDA in 2012 as an adjunct to caloric restriction and physical exercise for weight management in patients with BMI >30 or >27 with comorbidities (e.g., hypertension, diabetes, dyslipidemia). Lorcaserin is selective for 5-HT2C and may reduce risks associated with earlier medications of this group (such as hallucination, PAH and cardiac valvular insufficiency), Lorcaserin generates an annual weight loss of ~3.2–3.6 kg in addition to improved metabolic indices including blood pressure and blood lipids.

Liraglutide is a glucagon-like peptide-1 (GLP-1) agonist of an incretin-derived hormone which helps to control glucose homeostasis, and food intake, Liraglutide was initially developed for treatment of T2D given its incretin property. Liraglutide not only reduces glucose levels and promotes satiety but also retards gastric emptying and lowers bodyweight in a dose-dependent manner (628). It is the only injectable antiobesity medication that promotes weight loss by fostering satiety via hypothalamic stimulation and retarding gastric emptying. It is approved by FDA and EMA for patients with BMI >30 or >27 with obesity-related comorbidities.

Phentermine/topiramate is classified as a sympathomimetic that stimulates noradrenaline release and inhibits appetite, while topiramate is an anticonvulsant that maximizes body weight loss associated with phentermine use although the mechanism behind appetite suppression remains at large. It is considered an effective weight loss agent with reported 6.6–8.6 kg weight loss over a period of 12 mo.

Naltrexone/bupropion is an opiate antagonist, whereas bupropion is a weak dopamine and noradrenaline reuptake inhibitor. Monotherapy of these medications has been used for management of addiction to nicotine and alcohol. Not surprisingly, combination therapy was approved for the FDA and EMA to elicit central nervous system reward effects on food intake and satiety though antagonistic feedback inhibition. for obesity treatment. Naltrexone/bupropion promotes satiety via stimulation of POMC-mediated release of melanocyte-stimulating hormone (MSH) to lower food intake and facilitate energy expenditure. Naltrexone/bupropion is indicated for BMI >30 or >27 in association with at least one of the obesity-related comorbidities.

4.1.3.2. INSULIN SECRETAGOGUES. In addition to the FDA-approved antiobesity medications, a number of drugs commonly used in metabolic diseases such as T2D may also offer benefit in clinical obesity management. Dipeptidyl peptidase 4 (DPP-4) inhibitors are used through suppression of degradation of incretin hormones to maintain plasma glucagon-like peptide (GLP-1) and gastric inhibitory polypeptide (GIP) levels, resulting in facilitation of insulin secretion in pancreatic β cells and inhibition of glucagon release in pancreatic α cells as well as diverse GLP-1 biological response through GLP-1 receptor ubiquitously expressed in various tissues (632). More evidence has suggested that inhibition of DPP-4 using linagliptin improved obesity-associated insulin resistance and inflammation via intervening the M1/M2 macrophage phenotypical switch (633–636). Earlier evidence noted little adverse effects in body weight, ischemic incidence, heart rate and blood pressure in patients using DPP-4 inhibitors. Recent findings favor beneficial clinical outcomes of DPP-4 (637, 638). For example, risk of all-cause mortality may be drastically lowered when insulin is administered with DPP-4 inhibitors compared with insulin plus non-DPP-4 inhibitors (639).

4.1.3.3. POTENTIAL THERAPEUTIC TARGETS. 4.1.3.3.1. Autophagy. Both clinical and experimental findings support an essential role for autophagy in maintaining metabolic homeostasis in obesity (640). To this end, autophagy-targeting compounds have been applied in clinical or preclinical settings. It has been well documented that induction of autophagy is mainly derived from nutrient sensing signaling of mTOR, AMPK, and the insulin-IGF1 cascade (87, 133, 453). Hyperactivation of mTOR provokes metabolic derangement by suppressed autophagy (641). Therefore, nutrient sensing through mTOR is cardinal for metabolic regulation and serves as a likely target for intervention of autophagy in metabolic derangement and lysosomal dysfunction (642). For example, the transcriptional factor TFEB mediates mTOR phosphorylation to govern autophagy flux and sustained transcriptional regulation of autophagy (643). Many drugs with proven benefits in the therapeutics of obesity and T2D involve autophagy regulatory mechanism, including

metformin, thiazolidinedione pioglitazone, and DPP-4 inhibitors, as summarized in our recent review (133). Nonetheless, it is noteworthy that these metabolic regulatory medications may produce off-target effects thus it is premature to credit autophagy as their only and main mechanism for metabolic regulation in obesity.

4.1.3.3.2. Adiponectin. As an anti-inflammatory cytokine, chronic overexpression of adiponectin provokes abrupt rises in subcutaneous fat, and retards diet-induced insulin resistance (644). It was revealed that classical antidiabetic agents including PPARγ agonists (e.g., thiazolidinediones) are capable of stimulating circulating levels of adiponectin. More evidence has revealed beneficial effect of adiponectin in hepatomegaly, liver steatosis, and liver injury in obesity. Although the precise mechanism of action behind adiponectin-elicited metabolic benefit remains elusive, the ability of adiponectin to promote carnitine palmitoyltransferase I and hepatic FAO may play a role, with both enzymes or processes heavily involved in fatty acid synthesis (645).

4.1.3.3.3. Antiinflammatory agents. Obesity is commonly associated with a chronic low-grade inflammation. Not surprisingly, anti-inflammatory drugs are potentially effective in obesity, with low risks of adverse effects. Salsalate, a prodrug of salicylate to inhibit IKKβ/NF-κB, improves glycemic control in patients with T2D (646). Along the same line, inhibition of proinflammatory cytokines also shows promises in metabolic regulation. For example, IL-1 receptor antagonists (anakinra) have been shown to benefit glycemia and β-cell function (647). TNF-α blockade with etanercept, on the other hand, failed to display major response in insulin sensitivity although improvement on circulating inflammatory cytokines and glucose were noted (648).

4.1.3.3.4. Aldosterone antagonists: eplerenone. As mentioned earlier, Na retention is a central component of obesity-related HFpEF, where diuretics serve as a logical therapeutic regimen (322). Obese patients are usually responsive to diuretics albeit with worsened renal function following natriuresis. Given the overproduction of aldosterone in obesity due to hyperactivation of RAAS and adipokine leptin, Na retention in obesity may be better addressed using aldosterone antagonists. Moreover, adipocytes also synthesize aldosterone directly, and elevated neprilysin in obesity diminishes natriuretic peptide-induced suppression on aldosterone secretion. In addition to Na retention, hyperaldosteronism also promotes epicardial adipose tissue inflammation and therefore onset of microvascular rarefaction and fibrosis in myocardium. In this case, perivisceral fat transforms into a proinflammatory phenotype in a mineralocorticoid receptor-dependent manner (649). Recent work also implicates increased aldosterone and coronary artery MR activation in promotion of Western diet-induced cardiomyocyte stiffness and diastolic dysfunction (650).

4.1.3.3.5. PPARγ agonists thiazolidinediones. Drugs targeting on insulin secretion (secretagogues such as sulfonylureas and meglitinides) or insulin sensitivity [insulin sensitizers such as thiazolidinediones (TZDs) and metformin] are the mainstream therapeutic options for T2D. In particular, TZDs remain a first-line therapeutic option for T2D, courtesy of the antihyperglycemic properties elicited by PPARγ, which regulate essential genes involved in glucose and lipid metabolism.

Given that obesity is the single most independent risk factor for T2D, many pharmacotherapies employed in the management of T2D received some favorable indications in obesity including the FDA-approved antidiabetic drugs metformin, insulin therapy, PPARγ agonists sodium–glucose cotransporter 2 (SGLT2) inhibitors, sulfonylureas, meglitinides, dipeptidyl peptidase 4 (DPP-4), and inhibitors (589, 629, 651–653). Moreover, novel targets recognized in the therapy of T2D such as free fatty acid receptor 1 (also known as G protein-coupled receptor 40), glucokinase, and protein tyrosine phosphatase 1B have not been fully validated in the clinical management of obesity and obesity complications. Given the complexity and the multifactorial nature of obesity, a multitarget approach is worth of exploration (654).

4.1.3.3.6. Epigenetically based pharmacotherapy. Epigenetics has seen a drastic development over the last years although it remains challenging to apply effective epigenetically based pharmacotherapy for obesity probably due to incomplete picture of epigenome regulation by metabolic stress (655). This is particular helpful for early life deleterious epigenetic programming (656). Epigenetic therapies inhibiting DNA Methyltransferase DNA methyltransferases (DNMTs) or histone deacetylases (HDACs) have shown some promises. Three HDAC inhibitors, as well as two DNMT inhibitors are FDA-approved for cancer therapy (657). Several HDAC and DNMT inhibitors as well as candidates targeting ncRNAs are currently under preclinical studies. Despite the benefit for Na restriction and nutrient supplement to control DNA methylation, employment of such measures to control lipid and glucose levels in obesity is still debatable. One obvious disadvantage is the likely unspecific and profound epigenetic deregulation nature of these drugs. Generally speaking, epigenetic-based therapy offers a potential way to prevent and mitigate chronic diseases through altering or correcting epigenetic abnormalities (658). Higher levels of LDL particles and lower levels of HDL particles were noted in coronary heart disease in morbid obese postmenopausal women

(659). Circulating proinflammatory biomarkers offer potential utility in predicting the risk of coronary artery disease through its positive correlation with pericoronary fat (660). However, a number of drawbacks still hinder the clinical applications of these traditional biomarkers. Given the lack of efficient biomarkers for early diagnosis of cardiac anomalies and the emerging role of epigenetic traits in obesity, "BMI"-associated epigenetic biomarkers have gained some popularities in the early diagnosis and management of obesity-induced CVD. Genomic imprinting is a process of epigenetic modification which allows the gene to be expressed in a parent-of-origin specific manner. In this vein, investigators identified a nonclassical imprinted gene dysregulation in the Trim28 haploinsufficiency-induced obesity (661). This notion of alternate epigenetic trajectories in obesity points to a new direction for pharmacological drug development targeting the potential "on-and-off" switch for obesity phenotype manifestation.

4.1.4. Bariatric surgery.

In comparison to lifestyle interventions and pharmacological agents, bariatric surgery has long been established as a more effective and durable intervention for weight-loss and remission of cardiovascular risks (662, 663). Three major types of bariatric surgery are widely conceived (664). Laparoscopic adjustable gastric banding involves placing an inflatable silicone band around the upper stomach, without anatomical gut changes, to reversibly restrict the transit of ingested food. Roux-en-Y gastric bypass restricts food intake by reconstructing the alimentary canal, such that food bypasses majority of the gastrointestinal tract. The lately developed vertical-sleeve gastrectomy involves excision of more than half of the stomach to accelerate the gastric emptying. The use of the latter two procedures has escalated due to larger weight-loss (~25% and 30%, respectively) and less reoperation rates than gastric banding (662, 665).

With the well-perceived cardiovascular risks in obesity, proven clinical benefits are solidified for bariatric surgery, especially after Roux-en-Y gastric bypass and vertical-sleeve gastrectomy (666). At a 2-yr follow up, gastric bypass surgery reversed LV remodeling and preserved LV and RV function, along with weight-loss (300). Compared with gastric banding, Roux-en-Y gastric bypass restricts reduced more abdominal visceral fat and ameliorated LV remodeling and aortic stiffness caused by obesity (667). Furthermore, bariatric surgery leads to remission of obesity-related insulin resistance, hypertension, and other metabolic complications (665, 668). **TABLE 2** summarizes proven benefits of bariatric surgery on overweight- and obesity-induced cardiac remodeling and contractile dysfunction including reduced LV mass, wall thickness, as well as systolic and diastolic functional indices. Nonetheless, it is noteworthy that a cadre of clinical observations failed to note discernable changes in certain aspects (such as systolic or diastolic function) in obese individuals despite clear weight loss, indicating possible disparate response of weight loss on reversibility of cardiac remodeling and contractile dysfunction in obese individuals. Among the pleiotropic effects of bariatric surgery, complicated mechanisms that contribute to the prolonged cardiometabolic improvements following bariatric surgery include stable weight-loss, sustained satiety, subsequent changes in eating habits and gastrointestinal hormone activity, whereas further investigation is required (669).

As with all procedures, potential risks must be weighed against its benefits before proceeding with bariatric surgery. Limitations remain, including the high cost initially, potential risks for weight regain, surgical revisions, short- and long-term complications, and the lifelong requirement for nutritional supplementation (665). Furthermore, pharmacological intervention is still a viable approach to most cardiovascular anomalies. Collectively, Roux-en-Y gastric bypass and vertical-sleeve gastrectomy are feasible alternatives to the treatment of severe and/or refractory obesity, taking into account the potential risks and high cost.

5. SUMMARY AND CONCLUSION

Here we provided a contemporary review that iterates the evidence for the existence of an entity termed obesity cardiomyopathy and putative mechanisms from the perspectives of genetics and epigenetics for its pathogenesis, as well as therapeutic options/implications for this disorder. Clinical findings have underscored the presence of ventricular dysfunction in obesity independent of hypertension, coronary heart disease and other conventional causes of CVD. Experimental evidence has also confirmed pathophysiological changes in myocardial structure and function in genetically predisposed and diet-induced obesity. Contemporary understanding of the mechanisms underlying obesity cardiomyopathy include metabolic disturbances (insulin resistance, abnormal glucose transport, increased FAs, lipotoxicity, and amino acid derangement), changes in intracellular Ca^{2+} homeostasis, oxidative stress, autophagy dysregulation, myocardial fibrosis, cardiac autonomic neuropathy (denervation or adrenergic and renin-angiotensin aldosterone overflow), inflammation, small coronary vessel disease (microangiopathy), impaired coronary flow reserve, and coronary artery endothelial dysfunction. In addition, epigenetic modifications also participate in the etiology of obesity cardiomyopathy. Ample evidence has been engaged toward the management of obesity cardiomyopathy, although effective and targeted medications

and procedures are still lacking. Nonpharmacological approaches such as lifestyle modification (e.g., exercise and diet control) may also benefit heart health in obesity (670).

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DISCLOSURES

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AUTHOR CONTRIBUTIONS

J.R. and S.W. prepared figures; J.R., N.N.W., and J.R.S. drafted manuscript; J.R., N.N.W., S.W., J.R.S. and Y.Z. edited and revised manuscript; J.R., N.N.W., S.W., J.R.S. and Y.Z. approved final version of manuscript.

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