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Cardiovascular Consequences of Obesity and Targets for Treatment

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Abstract

Obesity is a risk factor for cardiovascular disease, including coronary artery disease and heart failure, but the mechanisms by which it may cause them are not completely clear. Currently, therapies aimed at obesity-related cardiovascular disease include weight loss strategies and reduction of the other risk factors that are associated with obesity and cardiovascular disease. Other pathways with for potential drug development for obesity-related CVD are also discussed.

Keywords

obesity; myocardium; metabolism; systolic function; diastolic function; coronary artery disease

Cardiovascular disease (CVD) is still the leading cause of death in developed countries, despite a recent decline in coronary artery disease-related deaths. In the United States approximately 35% of all deaths are due to CVD [1]. Obesity (defined as a body mass index [BMI] of ≥ 30 kg/m²) is a risk factor for CVD, especially coronary heart disease and heart failure. It is estimated that the relative risk of coronary heart disease in obesity is approximately 1.5 even after adjusting for all other traditional coronary heart disease risk factors that often co-migrate with obesity (e.g. hyperlipidemia, hypertension) [2]. Obesity also is associated with an increased risk of heart failure, with ~11 – 14% of all heart failure thought to be attributable to obesity [3]. Given that excess body weight now affects more than 300 million persons worldwide, prevention and treatment of obesity should be considered one of the cornerstones for the prevention of CVD

(<http://www.who.int/dietphysicalactivity/publications/facts/obesity/en/>). This review will focus on the impact of obesity on CVD, particularly atherosclerotic coronary artery disease and heart failure and treatment of obesity-related heart disease.

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Obesity and Atherosclerotic Coronary Artery Disease

There are multiple mechanisms by which obesity leads to atherosclerotic coronary artery disease. First, obesity is associated with multiple factors which are themselves major risk factors for atherosclerosis, including abdominal obesity, insulin resistance (and its ultimate form, type 2 diabetes), atherogenic dyslipidemia (i.e., high plasma triglyceride and low high-density lipoprotein [HDL]-cholesterol concentrations), and hypertension. These risk factors often cluster in what has been termed the “metabolic syndrome.” There is considerable controversy as to whether the metabolic syndrome itself is a distinct risk factor for CVD, or if it simply confers the risks associated with its parts. However, it is helpful to recognize that separate components of the metabolic syndrome often accompany obesity and may cluster together (Table 1). The metabolic syndrome is associated with increased risk of death from CVD even in the subset of patients without frank diabetes. In one large study, the overall hazard ratios for CVD mortality in those with metabolic syndrome were 2.26 and 2.78 in men and women, respectively [4]. This increased risk of cardiovascular and coronary heart disease in patients with the metabolic syndrome has been validated in at least 2 other large-scale trials [5].

Obesity and hypertension

One of the components of the metabolic syndrome that often tracks with obesity, and which is also a risk factor for CV disease, is hypertension. Data from population studies suggest that approximately 75% of hypertension can be attributed to obesity [6]. On average, for each increase of 10 kg of body weight there is an associated increase of 3.0 mmHg systolic and a 2.3 mmHg of diastolic blood pressure [7]. Although these blood pressure increases may at first appear minor they portend a 12% increase in coronary heart disease risk and a 24% increase in stroke risk [7].

The exact mechanisms for the relationship between obesity and hypertension are not completely understood, but it is known that adipose tissue can make angiotensinogen, angiotensin converting enzyme (ACE), and angiotensin receptor 1 (AT 1) [8,9]. Renin activity and aldosterone are also upregulated in obesity [10]. These alterations increase plasma volume and contraction of vascular smooth muscle, both of which may contribute to increased blood pressure. Obesity is also associated with an imbalance sympathovagal system, as shown by ganglionic nerve studies, heart rate variability studies, and renal norepinephrine spillover studies [11]. This increased activation of the sympathetic nervous system may also contribute to increased blood pressure in the setting of obesity due to the activation of β_1 -adrenoreceptors in the myocardium, leading to an increased left ventricular (LV) dP/dt (rate of rise of LV pressure). Increased sympathetic tone associated with obesity also may increase blood pressure via arterial vasoconstriction due to α_1 -adrenoreceptor stimulation. Lastly, obesity is associated with a low-grade systemic inflammatory state. Adipose tissue itself can manufacture the proinflammatory cytokines, interleukin-6 (IL-6), and tumor necrosis factor- α (TNF- α), and these can regulate other markers of inflammation, such as C-reactive protein (CRP) [12]. Data are now emerging that link this increased inflammation with increases in blood pressure [13]. Based on these mechanisms, treatment of obesity with weight loss is recommended as a first step by the 7th report of the Joint National Committee (JNC) on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (<http://www.nhlbi.nih.gov/guidelines/hypertension/express.pdf>). Weight loss is associated with an improvement in hypertension in a dose-dependent fashion [14]. For patients without other compelling indications, thiazide-type diuretics, ACE inhibitors, AT1 receptor blockers, and β -adrenergic blockers are also rational therapies to consider in the obese patient with hypertension based on the mechanisms described above, and all are listed as initial therapies for Stage 1 hypertension per the 7th JNC report.

Obesity and dyslipidemia

Dyslipidemia is another classical risk factor for CVD that often tracks with obesity, especially in obese patients who also have the metabolic syndrome. High triglycerides and low levels of high-density lipoprotein (HDL) levels are commonly seen with obesity. Low HDL is a risk factor for CVD in addition to the more commonly known lipid risk factor – increased low-density lipoprotein (LDL). Although there is more controversy regarding the cardiovascular risk associated with high triglycerides, there are now several large trials suggesting that they are a risk factor for CVD, particularly in women [15,16]. The increase in triglycerides appears to be at least in part due to an increase in fatty acid (FA) turnover and delivery to the liver resulting in an increase in very low-density lipoprotein (VLDL) production [17]. Insulin resistance (often accompanying obesity) lowers HDL levels partly due to increased apolipoprotein A-1 (a component of HDL) catabolism and HDL remodeling from increased hepatic lipase action [18]. HDL production from remnant particles of triglyceride-rich lipoproteins is also hindered by insulin resistance [19]. The fact that these lipid abnormalities (high triglycerides and LDL, and low HDL) generally improve with weight loss, further supports the idea that obesity is directly involved in the development of this particular type of atherogenic dyslipidemia [20].

Obesity and diabetes

There is no question that obesity is a risk factor for the development of type 2 diabetes, which in turn is one of the most virulent of CV risk factors. Although not all persons who are obese develop diabetes, almost 90% of patients with type 2 diabetes are at least overweight (www.naaso.org/information/diabetes_obesity.asp). Unfortunately, diabetes is associated with a markedly increased risk of CVD, such that it is the number one cause of death of persons with diabetes. Moreover, it is well established that there are sex-related differences in the manifestation of CVD in patients with diabetes, with women having a greater risk than men [21].

The mechanisms by which obesity contributes to diabetes, and hence CVD risk, are the subject of much research. Recent data suggests that adipose tissue is not simply an inert depot for excess calories but is metabolically active. It generates and exports inflammatory markers, hormones, and FAs that interact with other tissues. In particular, adipocytes appear to have a stress response to excess lipid, which causes the endoplasmic reticulum (the locus of protein production and folding) to undergo what has been termed the “unfolded protein response.” This response impairs insulin signaling, and hence insulin resistance, and, if prolonged, may result in apoptosis [22]. This process has also been implicated in the death of the insulin-producing pancreatic beta cells, which may also contribute to the development of type 2 diabetes. Studies in animal models also demonstrate toxic effects of elevated FA levels on beta cells (and other nonadipocytes) via a pathway known as “lipotoxicity” [23,24]. These pathways provide intriguing targets for future therapeutic interventions, in addition to the more traditional weight loss (discussed below) for the amelioration of obesity-related diabetes.

Obesity and endothelial function

Although not considered a traditional “risk factor” for the development of CVD, per se, endothelial dysfunction is an early marker of CVD and contributes to CV events. The vascular endothelium releases vasoactive relaxing and contracting factors that are important for the control of vascular tone. An imbalance in the factors controlling vascular tone may lead to vasoconstriction, vascular inflammation, thrombosis, and atherosclerosis. Increasing BMI predicts impaired endothelial function [25]. It is particularly prevalent in patients with visceral obesity and insulin resistance [26]. Unfortunately, the association between excess weight and endothelial dysfunction can present as early as childhood [27].

Obesity is thought to affect endothelial function predominately via co-morbidities, such as insulin resistance and dyslipidemia. Supporting this is the observation that obese individuals exhibit resistance to the vasodilator actions of insulin [28]. Furthermore, hyperglycemia and hyperlipidemia, often present in obesity, have been shown to impair nitric oxide (NO)-induced, endothelial-dependent vasodilation [29,30].

However, adipose tissue itself also appears to play an important role in the control of endothelial function because adipocytokines have vasoactive properties [31]. For example, adiponectin can accumulate in the vessel wall, exert anti-inflammatory effects, and enhance production of NO [32]. Unfortunately, obesity is associated with relative adiponectin deficiency, which thus may contribute to impaired endothelial function. Leptin's effects are more complicated since some studies demonstrate it enhances sympathetic tone while increasing NO production, and others show it improves endothelial- and NO-independent vasodilation [33,34]. Other cytokines from adipocytes, IL-6, FAs, are thought to decrease NO production and so, contribute to impaired endothelial function. Lastly, adipose-derived components of the renin-angiotensin system also contribute directly to vasoconstriction [35,36].

Obesity and atherosclerosis

A thorough review of the entire atherosclerotic process is beyond the purview of this review and has been described by Libby and others; however, in order to demonstrate obesity's effect on atherosclerosis, we will briefly outline the major events of atherosclerosis here [37]. One of the earliest events of atherosclerosis is endothelial damage and dysfunction [38]. Also early on, there is recruitment of blood monocytes, which attach to the endothelium via vascular cell adhesion molecule (VCAM)-1 and migrate to the subendothelial space of the artery wall, where they become tissue macrophages [37]. Low-density lipoprotein (LDL)-cholesterol also migrates into the subendothelial space and is modified by oxidation or glycation [37]. This modified LDL is then taken up by the scavenger receptors of the macrophages. Accumulation of lipid within the macrophages creates the "foam cell" – the hallmark of the early atherosclerotic plaque [37]. Foam cell breakdown, deposition of free cholesterol and its esters, smooth muscle cell proliferation, and deposition of calcium and collagen occur in the later stages of atherosclerosis [37]. Destabilization of the plaque via macrophage-derived matrix metalloproteinases contribute to plaque rupture that precedes thrombosis and infarction [37]. All of the other CV risk factors that track with obesity contribute to this process, and so obesity contributes to atherogenesis indirectly by contributing to these other risk factors.

Obesity also directly contributes to atherogenesis via the effects of some of the adipokines that adipose tissue generates. Specifically, interleukin-6 (IL-6), tumor necrosis factor (TNF)- α , angiotensin-II, and leptin, are all proinflammatory and are secreted by adipose tissue. IL-6 induces VCAM-1 expression and monocyte chemoattractant protein -1 secretion by endothelial cells, both of which encourage monocytes to attach to and infiltrate into the subendothelial space of the artery wall [7,37,39]. However, the effects of IL-6 on atherosclerosis are complex and not simply pro-atherosclerotic since results from studies in IL-6 murine knock-out models demonstrate that baseline, physiologic level of IL-6 may be necessary for normal vascular development and modulation of vascular remodeling [40]. Another inflammatory adipokine, TNF- α , also stimulates VCAM-1 expression, LDL uptake by macrophages, and promotes plaque destabilization [37,41,42]. Angiotensin II also stimulates VCAM-1 and MCP-1 expression, monocyte infiltration, and smooth muscle cell proliferation in the vessel wall [37]. Leptin also promotes atherosclerosis because leptin increases the accumulation of cholesterol esters in foam cells and promotes oxidative stress [43]. Adiponectin, an anti-inflammatory adipokine, on the other hand, is thought to stabilize atherosclerotic plaques via tissue inhibitor of metalloproteinase-1 (TIMP-1), inhibit transformation of macrophages to foam cells, and inhibit cell proliferation stimulated by

oxidized LDL [36]. Thus, the relative adiponectin deficiency associated with obesity also would promote atherogenesis and plaque formation. Inflammation and oxidative stress also appear to play a role in the vascular calcification that often is a relatively late finding in atherosclerosis [44]. Thus, pro-inflammatory adipokines may also affect this pathologic calcification process. In sum, obesity acts both indirectly and directly on the vasculature promoting atherosclerosis, one of the main pathophysiologic processes leading to coronary artery disease and its clinical sequelae.

Obesity and thrombosis

The final common event for most patients who have a myocardial infarction from atherosclerotic coronary disease is endothelial lining rupture and subsequent thrombosis, superimposed on an intracoronary plaque. Obesity is considered a prothrombotic condition due to increased activity of the coagulation cascade, which is not fully compensated by increased activity of the fibrinolytic cascade. Several studies have shown that the plasma concentrations of many prothrombotic factors (fibrinogen, vonWillebrand factor [vWF], factor VII, and plasminogen activator inhibitor-1 [PAI-1]) are higher in obese compared with normal weight individuals [26,45]. Plasma concentrations of antithrombotic factors, such as tissue-type plasminogen activator (t-PA) and protein C, are also increased, but not enough to counteract the increase in prothrombotic factors [45].

The increased thrombotic potential accompanying obesity is related, at least in part, to insulin resistance. Insulin resistance is associated with inflammation and oxidative stress, both of which are implicated in the generation of components of the thrombotic cascade. Resistance to insulin leads to thrombosis promotion because insulin is antithrombotic and profibrinolytic, suppressing 1) NF- κ B binding activity, 2) reactive oxygen species generation, 3) proinflammatory factors expression, and 4) PAI-1, tissue factor, and platelet activity [46].

Excessive adipose tissue also directly contributes to the imbalance between thrombosis and fibrinolysis because adipose tissue secretes multiple adipokines, cytokines, and hormones that are implicated in thrombosis. Leptin, resistin, PAI-1, tissue factor, angiotensin II, FAs, TNF- α , transforming growth factor- β , and IL-6 are all secreted by adipose tissue and are all implicated in thrombosis [26,45]. The general pathway through which these adipokines are thought to increase thrombotic potential is via inflammation and reactive oxygen species, which are known to lead to platelet activation and thrombosis [26]. Weight loss has been shown to improve this thrombotic tendency. Whether antioxidants have a beneficial effect on obesity-related thrombosis in humans is as yet unproven. Thus, obesity contributes indirectly to atherosclerotic CVD via increasing the incidence of other CV risk factors, and obesity contributes directly to atherosclerotic CVD via promoting atherogenesis and thrombosis.

Obesity and heart failure

Although obesity is a risk factor for coronary artery disease, and hence, ischemic cardiomyopathy, obesity is also a risk factor for nonischemic heart failure. Rarely, obesity is related with a pathologic condition, known as “Adipositas Cordis” wherein the myocardium is so filled with lipid that it actually floats in water [7]. The lipid in the heart can be from an infiltrative process, with adipocytes strands streaming in from the epicardial fat, and/or a metaplastic process in which myocardial cells are replaced by adipocytes [7]. However, even in obese subjects without this extreme pathologic phenotype, there are alterations in cardiac structure, function, and metabolism that are characteristic of obesity, which may all contribute to the development of heart failure.

Obesity and cardiac structure

Recent studies, using modern techniques to evaluate cardiac structure suggest that obesity, even in the absence of hypertension, first leads to concentric left ventricular remodeling, characterized by increased LV wall thickness relative to the LV end-diastolic dimension. This is best expressed as an increase in relative wall thickness ($= 2 \times \text{posterior wall thickness/LV end-diastolic dimension}$) and can be seen even in adolescents with obesity (Figure 1) [47]. In support of this concept, BMI was the only independent predictor of LV mass and relative wall thickness in 51 young women in a multivariate analysis [48]. These changes may be adaptive and perhaps initially represent a beneficial response to obesity; i.e., by increasing wall thickness, LV wall stress may be lessened. However, over time this adaptation likely becomes maladaptive since frank LVH may ensue, which is an independent risk factor for sudden cardiac death and is associated with diastolic and systolic dysfunction. Concentric LV hypertrophy is thought to develop into eccentric hypertrophy with increased duration of obesity, and consequent increased duration of LV volume overload [10]. This structural change from concentric to eccentric LV hypertrophy with its defining LV cavity enlargement often accompanies frank LV systolic failure [10]. Furthermore, systemic hypertension, which often accompanies obesity, facilitates development of LV dilatation and hypertrophy [10]. Increased LV mass also makes the subendocardium more susceptible to ischemia and increases the risk of sudden cardiac death [10].

Obesity and cardiac function

There is evidence that excess body weight itself, independent of other known cardiovascular risk factors and independent of atherosclerosis and myocardial infarction impairs both diastolic and systolic function [48,49]. Indeed, the risk of developing clinical heart failure is estimated to increase by 5%–7% for every 1 kg/m^2 BMI increase and is thought to contribute to 11–15% of all heart failure cases [3]. Consistent with this there are several studies using load-dependent measures demonstrating the detrimental effects of excess body weight on diastolic function as measured using traditional echocardiographic Doppler imaging [50–53]. There is also evidence that there are direct, load-independent effects of obesity on cardiac function. For example, in a cross-sectional study of obese nonhypertensive, nondiabetic young women, tissue Doppler measurements of diastolic function, which are thought to be relatively load-independent, were decreased as BMI increased [48].

The effects of obesity on LV systolic function are less clear-cut, with some studies demonstrating decreased, some showing increased, and some showing no effect on LV systolic function [48,53,54]. Part of the explanation for these discordant results is likely due to the load-dependent nature of many of the measurement methods, since an obesity-related increase in plasma volume may increase cardiac output via the Frank-Starling mechanism. Another reason for the difficulty in assessing LV systolic function in obesity lies in the methods for indexing it to body size. Thus, although stroke volume and cardiac output are often high in obesity, when they are indexed to body surface area, they may be high, normal, or low. To assess contractility in a more load-independent manner, we evaluated the tissue Doppler measure of systolic function, S_m , in young women with uncomplicated obesity and found that systolic function was worse as BMI increased [48]. Thus, the mechanisms responsible for the obesity-related impairment in heart function appear due to both alterations in load (volume and pressure) as well as load-independent alterations. There is an increase in load through an increase in plasma and blood volume via activation of the renin-angiotensin-aldosterone system [10]. Pathologic and calibrated integrated backscatter studies also suggest that there are textural alterations in the myocardium that may affect the viscoelastic properties of the myocardium, which may be load-independent [49]. Lastly, alterations in myocardial metabolism may also play a role in the development of cardiac dysfunction.

Obesity and myocardial metabolism

Animal studies suggest that alterations in myocardial metabolism contribute to cardiac dysfunction in obesity [23,55]. Normally, the myocardium is an omnivore, able to utilize multiple substrates for metabolism but in the postnatal, resting, fasted state it primarily uses FAs. In response to an increase in FA delivery, the myocardium typically increases beta-oxidation of FAs (Figure 2). This increase in beta-oxidation of FAs occurs in animal models of obesity, even before the onset of diabetes [56]. However, it appears that if excessive FA delivery to the myocardium persists, even the myocardium's great capacity for FA oxidation may be overwhelmed leading to increased FA storage (Figure 2). Although much of this excess lipid may be stored in a relatively neutral form such as triglycerides, some of the FAs that enter the cell may contribute to apoptosis, via lipotoxicity [23]. Studies in animal models show that lipotoxicity may occur via ceramide-dependent or -independent pathways [23,24]. In these animal models of lipotoxicity, the myocardial metabolic abnormalities precede cardiac dysfunction and are thought to contribute to it [23,55,57]. Whether this process also occurs in humans is the subject of intense investigation.

In a study of young women with uncomplicated obesity, our group found that myocardial FA uptake, utilization, and oxidation all were increased as BMI and whole body insulin resistance increased, paralleling what was found in animal models of obesity [56,58]. It appears that this increased FA oxidation capacity in humans may also be overwhelmed, as it can be in animal models because autopsy and magnetic resonance spectroscopy studies both demonstrate that in subjects with diabetes there is an increase in intramyocellular triglyceride compared with normal controls [59]. In addition, LV biopsies from human hearts undergoing LV assist device implantation for heart failure demonstrate that patients with obesity or diabetes and heart failure have more accumulation of lipid within the myocardium than those with heart failure from other causes [60]. Also more indirectly supporting the theory that excessive FAs may contribute to LV dysfunction in obesity are results from a study relating plasma free FAs an LV diastolic dysfunction [61]. Further studies, including longitudinal and interventional studies are still needed in humans to prove that lipotoxicity occurs as it does in animal models.

Excessive myocardial FA metabolism may also contribute to cardiac dysfunction via increased free radical production. In obesity, with its inherent increase in FA oxidation, there is increased myocardial oxidative stress [62]. In animal studies free radicals appear to impair both vascular and LV systolic and diastolic function since decomposition of free radicals lead to improvement of these parameters [63]. Supporting this theory that not all of the cardiac dysfunction that is seen with obesity is due to apoptosis-related injury, are studies showing improvement in cardiac function after significant weight loss [64,65]. If myocardial cell loss were the only mechanism by which cardiac function were decreased, it would be unlikely to improve after weight loss.

Lastly, increasing BMI is an independent predictor of increasing myocardial oxygen consumption and decreasing efficiency both in animal models and in a recent study in young obese women [58,66]. Decreased efficiency may contribute to impaired ATP production, thereby hindering cardiac function, and decreased efficiency is a hallmark of heart failure.

Therapies for obesity-related CVD

Further supporting the theory that obesity has direct detrimental effects on CVD is the fact that there is accumulating data demonstrating that weight loss improves many obesity-related cardiac conditions. Conventional treatment for obesity includes diet, exercise, pharmacotherapy, and bariatric surgery. Weight loss by these methods generally results in improvement in CV risk factors such as hypertension, diabetes, and dyslipidemia [67]. Although the improvements in some of the CV risk factors that can be expected through weight loss (such hypertension) may appear to be minor (approximately 5–20 mmHg/10 kg) [68], they

are nonetheless sufficient to produce dramatic reduction in adverse cardiac events and stroke [69]. The particular type of diet (e.g., low-carbohydrate or conventional high carbohydrate, low-fat, low-calorie) used does not appear to affect the benefits of weight loss on plasma lipids, diastolic blood pressure, and insulin sensitivity as much as the weight loss itself [67]. Bariatric surgery has also been shown to improve CV risk factors [70]. In contrast, weight loss due to liposuction of subcutaneous fat does not result in improvement of the CV risk factors insulin sensitivity, blood pressure, or dyslipidemia, suggesting that loss of the more metabolically active visceral fat via the conventional methods listed above is more important than simply loss of adipose mass [71].

Similarly, life-style intervention appears to be a powerful tool to improve endothelial function [32] and to reduce the thrombotic potential [26]. More importantly, 2 large-scale, long-term studies of bariatric surgery-induced weight loss have been shown to decrease mortality due to heart disease and total mortality [72,73]. Thus, weight loss is considered an important tool for the control of CV risk factors, the atherogenic and thrombotic processes, and amelioration of coronary atherosclerosis-related morbidity and mortality.

LV structure and function, separate from coronary artery disease-related changes, also improve with weight loss. The more dramatic the LV remodeling pre-weight loss and the greater the weight loss (such as that achieved by bariatric surgery) the more likely the salutary effects of weight loss will be seen on LV remodeling. For example, in one study of obese patients bariatric surgery-related weight loss decreased LV mass and in those with a dilated LV pre-operatively, surgery also improved LV cavity dimensions [65]. More moderate weight reductions may also have beneficial effects on LV morphology. Diet therapy alone has been shown to improve LV internal dimensions, wall thickness, and mass. Diet plus exercise-induced weight loss also improved LV cavity size and LV mass [74]. Pharmacotherapy with sertraline has also been shown to have beneficial weight-loss-induced effects on LV mass and mass index [75].

LV function, both diastolic and systolic, also may benefit from weight loss in obese patients [64]. Some of these improvements may be in part due to salutary effects on CV hemodynamics, including a decrease in blood volume and mean arterial pressure [10]. However, it is likely that there are also direct effects on LV function as well since relatively load-independent echocardiographic studies have shown improvements in LV diastolic function and myocardial texture after weight loss [64,76]. Lastly, there are preliminary data suggesting that myocardial oxygen metabolism requirements per gram of LV tissue may improve with weight loss [77]. Thus, although there are observational studies that suggest that obese subjects fare better than nonobese counterparts after the onset of CVD, whether coronary-related or not, there are clear data demonstrating that maintenance of a normal weight helps prevent CVD and bariatric surgery-induced weight loss relates to an improvement in CV-related mortality. Hence, maintenance of normal weight and improvement of obesity still remains part of the standard of care for the prevention and treatment of CVD.

Risks of weight loss

Although moderate weight loss is generally well-tolerated, there are risks, particularly with rapid and marked weight loss. Weight loss via starvation, liquid protein diets, very low calorie diets, and bariatric surgery may be accompanied by prolongation of the QT_c interval [7]. Liquid protein diets in particular, have been associated with life-threatening arrhythmias [7]. Fenfluramine and dexfenfluramine, which have also been used in the past for weight loss, have been taken off the market because of reported valve disorders and pulmonary hypertension. Sibutramine and orlistat are currently available for the treatment of obesity; the former acts on the central nervous system and the latter acts in the gut to reduce fat, and hence calorie, absorption. Sibutramine, however, is not recommended for weight loss in patients already diagnosed with CVD because increases in blood pressure and heart rate may occur with this

drug [7]. The CV effects of the newer endocannabinoid receptor blockers have not yet been studied over the long-term.

New directions in drug therapy development

Clearly, treatment of the underlying cause of obesity-related CVD, i.e., obesity, remains the number one goal for prevention and treatment of obesity-related CVD. There are several approaches to obesity treatment (and prevention), which are outlined in Table 2. The options listed here range from current treatments such as appetite suppression, to more novel therapies that are being explored for potential future use, e.g., alteration of the gut microbiota to lessen food absorption [78]. It is also recommended that physicians screen for and treat the other CV risk factors that often track with obesity (diabetes, hypertension, and dyslipidemia) in order to lessen obesity-related CVD morbidity and mortality. The fairly recent discovery of adipokines, and elucidation of their effects and mechanisms of action has opened up a new potential field for drug therapy development. Interruption of the obesity-related inflammatory and oxidative stress pathways as well as myocardial metabolism modulation are all attractive new areas for development of new therapies aimed at ameliorating obesity's detrimental effects on the heart.

Conclusions

The epidemic of obesity that is increasing worldwide threatens to contribute to a decrease in life expectancy. Obesity, and the cardiovascular risk factors that often track with it, contribute to the number one cause of death in developed nations: CVD. Unfortunately, obesity has proven to be difficult to treat successfully in the long-term. Continued use of conventional weight loss methods and development of new therapies aimed at untraditional pathways of nutrient management and suppression of adipose-derived inflammation and oxidation will be necessary if we are to stem the growing pandemic of obesity-related CVD.

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Figure 1.

This diagram depicts short-axes views of the progression of LV remodeling that occurs with obesity. The first change shown in the upper right cartoon is an increase in the relative wall thickness (RWT) due to concentric left ventricular (LV) remodeling. RWT is calculated as $2 \times \text{the LV posterior wall thickness (grey arrow)} / \text{the LV cavity end-diastolic dimension (thin black arrow)}$. Next, frank LV concentric hypertrophy with increased LV mass and RWT may occur (bottom right), and lastly, increased LV mass and normal or decreased RWT may decrease and may be accompanied by heart failure and systolic dysfunction (bottom left).

Figure 2.

These positron emission tomography (PET) images and corresponding drawings demonstrate the importance of increased delivery of FAs to the myocardium in determining its metabolic profile. Increased FA β -oxidation is an early finding in the myocardium of obese subjects.

Table 1

ATP-III Criteria for the Metabolic Syndrome – Any 3 of the Following (Adapted from <http://www.nhlbi.nih.gov/guidelines/cholesterol/atglance.htm>)

Abdominal obesity
Waist circumference
>102 cm men
>88 cm women
Atherogenic dyslipidemia
Triglycerides >150 mg/dL
Low HDL
<40 mg/dL men
<50 mg/dL women
Insulin resistance or glucose intolerance
Fasting glucose >110mg/dL
Increased blood pressure
>130/≥85 mmHg

Table 2
Targets for the Prevention and Treatment of Obesity-Related CVD

1. Treatment/prevention of obesity

- Decreased food intake
 - Diet
 - Central nervous system (CNS) acting drugs
 - Drugs interacting in the Ghrelin/CNS axis
- Increasing substrate use
 - exercise
 - increasing oxidation,
 - PPAR- α agonists
 - uncoupling
 - Uncoupling protein modulators
 - or storage in metabolically less active depots
 - PPAR- γ agonists
 - Oleate [59]
- Altering nutrient absorption
 - New bariatric surgical treatments
 - Orlistat
 - Altering the microbiota of the gut [60]

2. Treatment of other obesity-related CVD risk factors, atherogenesis, and thrombosis

- Diabetes, hypertension, dyslipidemia

3. Suppression of the hormonal and/or cytokine effects of obesity

- Decreasing production of angiotensinogen, and other proinflammatory, pro-atherogenic, and pro-inflammatory adipokines and cytokines
- Enhancing the effects of the anti-inflammatory insulin-sensitizing adipokines
- Insulin sensitization

4. Treatment of obesity-related inflammatory and/or oxidative stress pathways

- Decreasing the effects of TNF- α , IL-6
- Antioxidants

5. Treatment of obesity-related myocardial metabolic abnormalities

- Improvement of efficiency
 - Substrate preference modulation
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