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REVIEW

Adiponectin, Leptin and Cardiovascular Disorders

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ABSTRACT: The landmark discoveries of leptin and adiponectin firmly established adipose tissue as a sophisticated and highly active endocrine organ, opening a new era of investigating adipose-mediated tissue crosstalk. Both obesity-associated hyperleptinemia and hypoadiponectinemia are important biomarkers to predict cardiovascular outcomes, suggesting a crucial role for adiponectin and leptin in obesity-associated cardiovascular disorders. Normal physiological levels of adiponectin and leptin are indeed essential to maintain proper cardiovascular function. Insufficient adiponectin and leptin signaling results in cardiovascular dysfunction. However, a paradox of high levels of both leptin and adiponectin is emerging in the pathogenesis of cardiovascular disorders. Here, we (1) summarize the recent progress in the field of adiponectin and leptin and its association with cardiovascular disorders, (2) further discuss the underlying mechanisms for this new paradox of leptin and adiponectin action, and (3) explore the possible application of partial leptin reduction, in addition to increasing the adiponectin/leptin ratio as a means to prevent or reverse cardiovascular disorders.

Key Words: adiponectin ■ cardiovascular diseases ■ hypoadiponectinemia ■ leptin ■ obesity

OBESITY AND CARDIOVASCULAR DYSFUNCTION

Currently, the increasing rate of obesity rises steeply and now reaches global pandemic proportions.[1] Obesity is one of the major health issues and is a crucial contributor to the global burden of chronic disease and disability. Obesity positively correlates with various metabolic challenges, including insulin resistance, type 2 diabetes, nonalcoholic fatty liver disease, cardiovascular dysfunction, and certain types of cancers.[2] The health consequences of such metabolic dysfunctions range from reduced quality of life to premature death. Of particular concern is the increased incidence of cardiovascular dysfunction, a group of diseases of the heart and blood vessels, mainly including coronary heart disease, cerebrovascular disease, peripheral arterial disease, rheumatic heart disease, congenital heart disease, deep vein thrombosis, and pulmonary embolism; it is the leading cause of death for individuals of most racial and ethnic groups in the United States.[3] Early-childhood obesity by 11 to 12 years, is positively associated with the development of cardiovascular dysfunction, highlighting the crucial link to obesity.[4] The identification of the key causative factors that mediate obesity-associated cardiovascular disorders is an urgent and still unmet need, even though this has been extensively explored over the past 2 decades.[5] Much interest has been directed towards a better understanding of the pathological expansion of fat mass, which may represent a crucial link between obesity and cardiovascular disease.[6]

THE INHERENT HETEROGENEITY OF ADIPOSE TISSUE

Adipose tissue shows a high degree of heterogeneity.[7] This is reflected by many aspects, such as the different adipose tissue depots located throughout the body, their unique individual cellular characteristics of the adipocytes and their diverse cellular composition.[8] Simply based on its location, adipose tissue can be subdivided into numerous categories. These include depots in subcutaneous, visceral, supraclavicular, anterior cervical, axillary, anterior subcutaneous, suprascapular, supraspinal, ventral spinal, infrascapular, dermal, pericardial and perirenal regions.[9,10] Of note, due to their close proximity to organs critically involved in the pathophysiology of the cardiovascular

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Nonstandard Abbreviations and Acronyms

AdipoR	adiponectin receptor
AdipoRon	an AdipoR1 and AdipoR2 agonist
CB1	cannabinoid receptor 1
CRP	C-Reactive Protein
db/db mice	mice deficient in leptin receptor
HMW	high molecular weight
LepRb	Leptin receptor isoform b
ob/ob mice	mice deficient in leptin
PPAR	peroxisome proliferator-activated receptor
ROS	reactive oxygen species
SGLT-2	sodium-glucose-linked transporter-2
STAT3	signal transducer and activator of transcription 3

system, the pericardial depot is closely associated with cardiovascular function.[11] Moreover, in rodents, fat-depots display a high degree of topological similarity to the depots in humans.[10] This adds much credibility to the use of murine model systems to study the progression of obesity in humans. Nevertheless, despite sharing a similar location, rodent and human retroperitoneal fat depots show some differences. In humans, the retroperitoneal fat often encapsulates the kidney, adheres tightly to the renal capsule and invades the renal sinuses; while in the mouse, this fat depot simply surrounds the kidney.[12] Beyond the differences in location, adipose tissue also has a complex cellular composition. The various depots consist of mature adipocytes, mesenchymal progenitor/stem cells, preadipocytes, endothelial cells, mural cells, T cells and macrophages.[13,14] Different cellular populations within adipose tissue have very distinct functions. For example, preadipocytes can be differentiated into mature adipocytes by providing a classical differentiation cocktail. It is this population of cells that are the major source for generating new mature adipocytes.[15] Endothelial cells share the same progenitor cells with mature adipocytes, and endothelial cells can be rapidly incorporated into vessels; for instance, to promote both postischemic neovascularization in nude mice and vessel-like structure formation in Matrigel plugs.[16] Endothelial cells also play an important role in the development of insulin resistance.[17] As such, a better understanding of adipose tissue heterogeneity will certainly help identify the critical players in mediating adipose tissue-associated cardiovascular disorders.

Adipose tissue has the unique ability to expand to an almost unlimited extent, despite not being transformed.[18] In response to excess energy supply, adipose tissue undergoes complete remodeling. This involves activation of a highly coordinated process among several cell types, including mural cells, macrophages and preadipocytes.[19] How this remodeling occurs during expansion is the key difference between healthy adipose tissue expansion versus unhealthy expansion. Failure to adequately remodel while expanding results in chronic, unresolved inflammation and metabolic dysfunction.[19–21] The expansion of adipose tissue can occur via 2 distinct mechanisms: (1) the increase in adipocyte size (hypertrophy), or (2) the generation of more adipocytes through precursor cell differentiation, a process termed adipogenesis (hyperplasia).[22] Hypertrophy, with larger adipocytes, is associated with a poor metabolic response, which includes unleashed lipolysis, altered patterns of adipokine secretion and enhanced proinflammatory cytokine secretion.[23] In contrast, hyperplasia is a much healthier form of adipose tissue remodeling, which generates many new, smaller adipocytes through recruitment and differentiation of preadipocytes.[24] In response to chronic metabolic challenge, such as high-fat diet feeding, both forms of adipose tissue remodeling can effectively be monitored and tracked in various fat-depots, by using the Adipo-chaser mouse model system.[25] This allows us, for the first time, to clearly differentiate between preexisting and new adipocytes in response to any kind of metabolic challenge.

The quantity and quality of adipose tissue are equally important in light of the obesity-associated increased risk for many accompanying health issues.[26] Too little adipose tissue, resulting from chronic weight loss or genetic issues in fat development, leads to severe congenital or acquired lipoatrophy.[27] The latter is a classical disorder that is characterized by insulin resistance, hypertriglyceridemia, nonalcoholic fatty liver disease, and cardiovascular disorders. In light of the continuum between lipoatrophy and obesity, maintaining the proper amount of adipose tissue mass is clearly crucial in preventing multiple metabolic sequelae of dysfunctional adipose tissue, such as cardiovascular disorders. Even with comparable amounts of adipose tissue, obese individuals display a range of metabolic phenotypes. The majority of obese individuals develop insulin resistance, hypertriglyceridemia, liver steatosis, hypertension, and cardiovascular disorders. However, a subset of obese individuals maintain a high degree of insulin sensitivity, thus rendering protection from various metabolic disorders. This favors the idea of metabolically healthy obesity, in contrast to metabolically abnormal obesity.[28,29] This idea is well established in clinical observations and strongly supported by rodent studies.[30–33] Much remains to be done to delineate the exact mechanisms that determine these dramatic metabolic differences. Over the decades, numerous studies have demonstrated that adipose tissue fibrosis and adipokine production are key determinants of pathological metabolic sequelae. This indicates that not only quantity, but also the quality of adipose tissue is equally important in exerting its effects.[34]

Historically, adipose tissue was predominantly viewed as a relatively inert energy reservoir. In fact, having

vast energy stores is an advantage for survival during reduced caloric availability. However, in more recent times of fuel surplus, the role of adipose tissue as an energy store was less of a research focus. As such, for many decades, the overall interest of adipose tissue was somewhat overlooked. The discoveries in the 1990s of leptin and adiponectin revitalized and helped reshape adipose tissue from simply being an energy reservoir, to a sophisticated and highly active endocrine organ. This opened a new era of exploring adipose tissue-mediated crosstalk with other organs.[35,36] In addition to leptin and adiponectin, adipose tissue secretes a large panel of other adipokines, cytokines, metabolites, and exosomes. Together, these form a unique secretome response that mediates inter-organ communication. This concept has been covered in our recent review.[37] Here, we will focus on leptin and adiponectin and their roles in cardiovascular function.

LEPTIN

Leptin was discovered in 1994[36] as a 16 kDa nonglycosylated protein that is predominately secreted from adipose tissue.[38] Other tissues, including skeletal muscle,[39] gastric mucosa,[40] placenta,[41] heart, mammary, and salivary glands[42] can produce small amounts of leptin under certain conditions. However, adipose tissue seems to be the predominant source for circulating leptin. This is due to the fact that deletion of the *Lep* gene exclusively in adipose tissue, leads to undetectable levels of the protein in circulation.[43] The circulating levels of leptin are highly proportional to the amount of adipose tissue mass, that is, the higher the fat mass, the higher the circulating levels of leptin.[44] For instance, female subjects, with overall larger relative fat mass, tend to exhibit 2-fold higher leptin levels in circulation, when compared with males of similar body weight.[38]

As a pleiotropic hormone,[45] leptin regulates many physiological processes, including food intake, nonshivering thermogenesis,[46,47] reproduction, hemostasis, angiogenesis, arterial pressure control,[48] and neuroendocrine and immune function.[49] To fulfill its physiological role, leptin must bind to the LepRb (long isoform of its receptor), which is highly enriched in the hypothalamic region of the brain and to a lesser extent in peripheral tissues and macrophages.[50,51] To date, it is still unclear what the precise leptin-sensing mechanism is, that is, how and when the central nervous system communicates to the peripheral tissues in response to leptin, and vice versa. Two prevailing models have been proposed.[52] In the first model, the levels of adipocyte-derived leptin in circulation are proportionally increased with the increase in fat mass. It is both these factors that activate a response from the central nervous system, which ultimately prompts a corresponding increase in energy expenditure, concomitant with a reduction in food intake.[52] Firm evidence of this model lies in the fact that elevating the levels of leptin in young mice, in a dose-dependent manner, reduces food intake and increases core body temperature.[53] In contrast, the second model builds upon the notion that the signal sensed, is actually a drop, rather than an increase in leptin. This drop in leptin levels prompts a physiological response in energy regulation and reproduction.[54] The latter model is best demonstrated by starvation-induced leptin reduction and its associated physiological response, which can be largely reversed by exogenous leptin supplementation. Both models are well supported by numerous experimental observations. As such, it is difficult to argue which model is superior to the other. Given that the common factor in the 2 models is a change in circulating leptin levels, we believe that leptin oscillations, within their physiological range, are the critical determinant of leptin's overall function. On a daily basis, the circulating levels of leptin are relatively stable. As such, this argues against a physiological role for leptin in regulating acute daily food intake.[55] Rather, in subjects of normal body weight, a high-fat meal can typically trigger postprandial changes in the circulating levels of leptin. Conversely, in obese individuals, this postprandial response in leptin levels is significantly flattened and delayed.[56]

LEPTIN'S PARADOXICAL EFFECTS ON CARDIOVASCULAR DISORDERS

Given the robust effects of leptin on food intake and energy expenditure, leptin therapy (by exogenously increasing circulating leptin levels) once promised to be a cure for diet-induced obesity and its associated metabolic disorders.[57] However, obesity-associated hyperleptinemia and leptin resistance rendered leptin therapy largely ineffective for the treatment of diet-induced obesity.[58] In the context of cardiovascular function, leptin exerts both dichotomous and paradoxical effects (Figure 1). In most cases, hyperleptinemia is positively correlated with unfavorable outcomes in cardiovascular disorders.[59,60] However, under some circumstances, leptin can elicit cardioprotective effects, by reducing cardiomyocyte hypertrophy and apoptosis.[61]

A fully intact leptin system exists in all regions of the heart; this includes leptin synthesis and a fully functional long form of its receptor.[62] As such, leptin signaling is necessary and indispensable for maintaining normal cardiac function. In young healthy men, a beneficial inverse correlation between measures of carotid wall thickness and circulating leptin is evident; thereby supporting a vascular protective role for leptin.[63] A deficiency in leptin itself (ie, *ob/ob* mice), or its receptor (ie, *db/db* mice) results in massive obesity and severe cardiovascular dysfunction.[64] The addition of leptin to *ob/ob* mice essentially restores normal thickness of the left ventricle; with this effect being independent of body weight.[65] Furthermore,

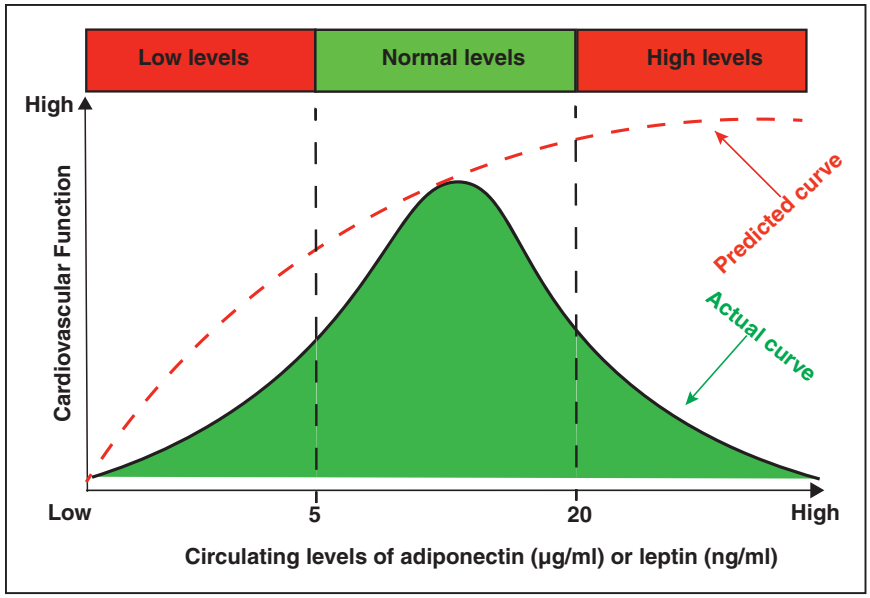

Figure 1. The paradoxical effects of adiponectin and leptin in regulating cardiovascular function.
Low levels of adiponectin and leptin are positively associated with severe cardiovascular disorders. Thus, it is predicted that high adiponectin and high leptin levels, beyond physiological (normal) levels, could greatly improve cardiovascular function, as shown by the red dashed curve. However, in most cases, high circulating leptin and adiponectin levels do not show any beneficial effects. Rather, both can be detrimental for cardiovascular function, similar to the conditions with low circulating levels, as shown in the green area, referred to as paradoxical effects.

restoring leptin receptor expression exclusively in cardiac tissue in *db/db* mice, reduces cardiac triglyceride content, to consequently improve cardiac function.[66] The complementary experiment, that is, a deletion of leptin receptors specifically in cardiomyocytes, leads to cardiovascular issues, which include impaired cardiac energy production[67] with an exacerbation in ischemic heart failure.[68] Leptin-activated STAT3 (signal transducer and activator of transcription 3) mediates the majority of leptin's physiological downstream signaling.[69] Mice harboring a deletion of STAT3 specifically in cardiac tissue are significantly more susceptible to cardiac injury following doxorubicin treatment; as a result of enhanced inflammation and cardiac fibrosis.[70] In addition, leptin conveys robust antiapoptotic effects in cardiomyocytes. In vitro, leptin treatment protects cardiomyocytes from apoptosis; potentially through its actions on improving mitochondrial function and reducing oxidative stress.[71,72] Of note, local overexpression of leptin (by using a recombinant adenovirus expressing the leptin cDNA), prevents lipotoxic cardiomyopathy in acyl-CoA synthase transgenic mice,[73] potently highlighting the antilipotoxic effects of leptin. Finally, leptin administration during reperfusion post ischemia significantly reduces infarct size.[74] Taken together, all these observations point at a substantial cardioprotective role for leptin. In addition, leptin plays an important role in regulating basal cardiac contractile function, as leptin-deficient *ob/ob* mice display impaired cardiac contractile function in ventricular myocytes.[75] Moreover, in an ex vivo system with cultured ventricular myocytes, leptin suppresses cardiac contractile function through the endothelin-1 receptor and reduced nicotinamide adenine dinucleotide phosphate oxidase-mediated pathway.[76,77]

In contrast to the beneficial effects, in the majority of cases, leptin, particularly in the context of obesity-associated hyperleptinemia, exerts detrimental effects in cardiovascular function and promotes adverse outcomes in cardiovascular disorders (Figure 2). In a large-scale epidemiological study, clinical observations revealed a positive correlation between hyperleptinemia and adverse cardiovascular outcomes.[78,79] High plasma levels of leptin were shown to predict short-term occurrence of cardiac death and stroke in patients with coronary artery disease; independent of established risk factors.[80] Moreover, increasing the serum concentrations of leptin positively correlates with the total number of stenotic coronary arteries; with serum leptin levels predicting the development of arterial stiffness in patients with coronary artery disease.[81] Independent of traditional risk factors (such as fasting insulin and CRP [C-reactive protein]) and metabolic abnormalities, hyperleptinemia is considered a better predictor of vascular compliance in adolescents.[82] Furthermore, leptin is an important cardiovascular disorder marker in the obese population; this can contribute to the evaluation of metabolic risk in these individuals.[83] Beyond these clinical observations, rodent models have offered great insight and improved understanding toward the underlying mechanisms related to the action of leptin. Raising plasma leptin levels, by either administration of exogenous leptin or ectopic overexpression of leptin, increases arterial pressure and heart rate; this eventually leads to hypertension.[84] Cardiac leptin overexpression, in the context of acute myocardial infarction and reperfusion, potentiates myocardial remodeling and left ventricular dysfunction.[85] In contrast, the local administration of a leptin antagonist attenuates angiotensin II-induced ascending aortic aneurysms and cardiac remodeling.[86] Consistent with these observations, leptin receptor-neutralizing antibodies improve cardiac function; this offers strong evidence that endogenous leptin is a driver for cardiac hypertrophy.[87] Several mechanisms may underlie the causative effects of leptin-induced cardiovascular disorders.[88] These include induction of the the mammalian target

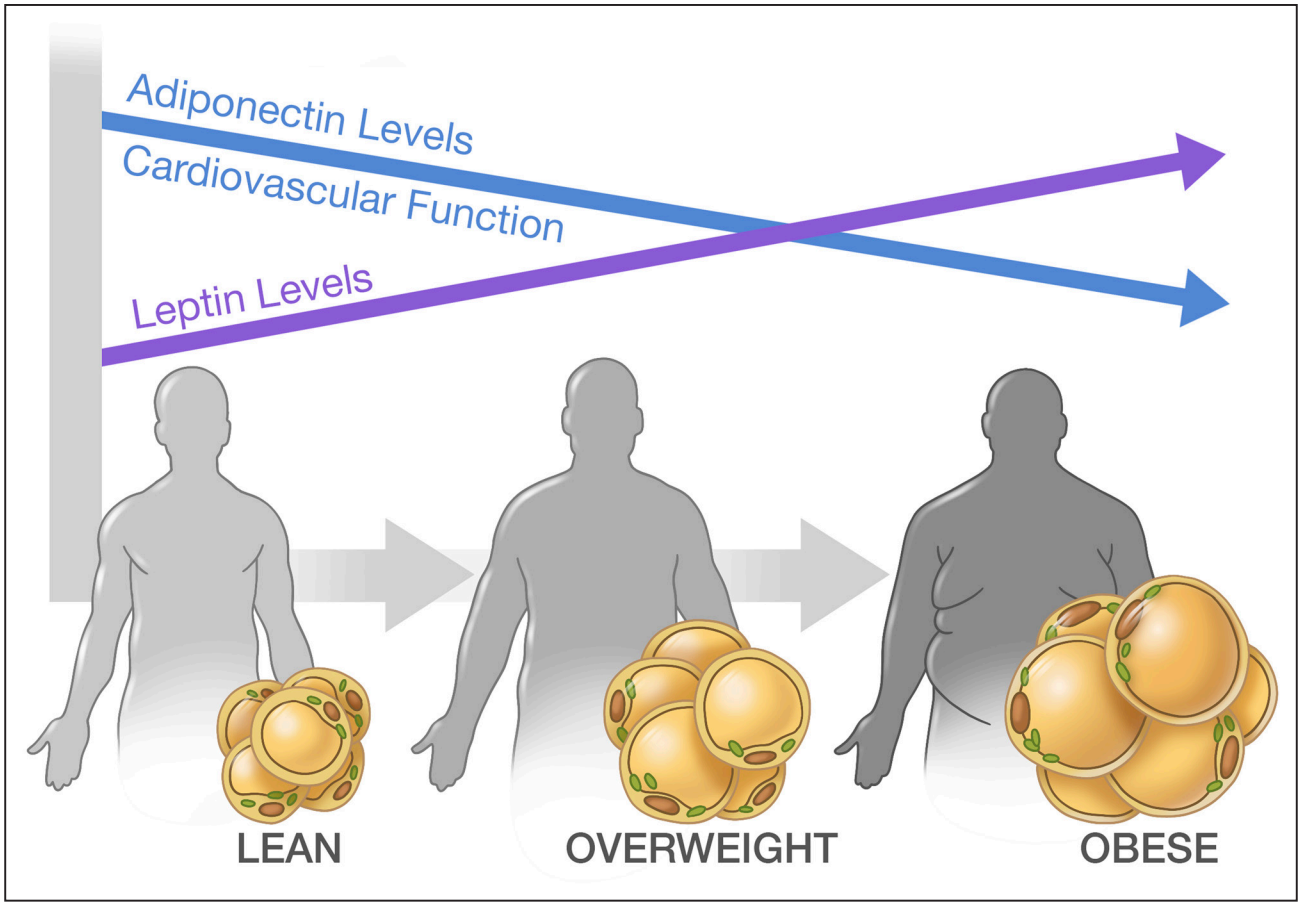

Figure 2. Relationship between body weight, fat mass, circulating leptin, and adiponectin levels with cardiovascular function. The gradual transition from lean to overweight to obesity is associated with dramatic adipose tissue expansion. During this process, circulating leptin and adiponectin levels are altered accordingly. Low adiponectin and high leptin levels eventually negatively affect cardiovascular function.

of rapamycin pathway, activation of PPAR (peroxisome proliferator-activated receptor) α signaling, increased production of reactive oxygen species, and the activation of p38 mitogen-activated protein kinase.[88]

A UNIFYING MODEL TO EXPLAIN THE PARADOXICAL EFFECTS OF LEPTIN ON CARDIOVASCULAR DYSFUNCTION

To date, there are no prevailing models to explain the seemingly paradoxical effects of leptin on cardiovascular function. Our recent observations on the effects that leptin has on body weight regulation offer a novel perspective to rationalize these paradoxical effects on the heart and vasculature. In the context of leptin sensitivity, primarily evident in young and lean mice, reducing circulating levels of leptin paradoxically results in a significant increase in food intake and body weight gain. This is, in fact, consistent with the existing models detailing the response to lower leptin concentrations. However, a different response is observed under conditions of leptin resistance. Here, a partial leptin reduction triggers a higher degree of leptin sensitivity, enhanced insulin sensitivity, with a reduction in body weight; an unexpected and surprising response to reduced leptin levels.[89–91] This seemingly paradoxical response to leptin reduction, in the general area of weight maintenance and energy expenditure, could also be critical for a better understanding of the paradoxical effects of leptin on cardiovascular function. Moreover, under obesogenic conditions, hyperleptinemia per se is sufficient to promote leptin resistance[91,92]; resulting in all the other metabolic disorders frequently associated with weight gain. Thus, circulating leptin levels, in a first approximation, reflect the state of an individual's leptin sensitivity: that is, higher circulating levels of leptin equate to lower leptin sensitivity. Based on these observations, here, we put forth a new model, in which properly sustained leptin signaling, within a narrow range, is essential for normal cardiac function (Figure 3). Deficiencies in the cardiac leptin signaling pathway, as observed in *ob/ob* mice and *db/db* mice, consequently result in cardiovascular dysfunction. In contrast, chronic overactivation of the leptin signaling pathway, as observed in the diet-induced obese mice, leads to obesity-associated cardiovascular disorders. In the latter model, the beneficial impact that leptin exerts on cardiac function also follows the general rule of leptin's involvement in metabolism, that is, "less

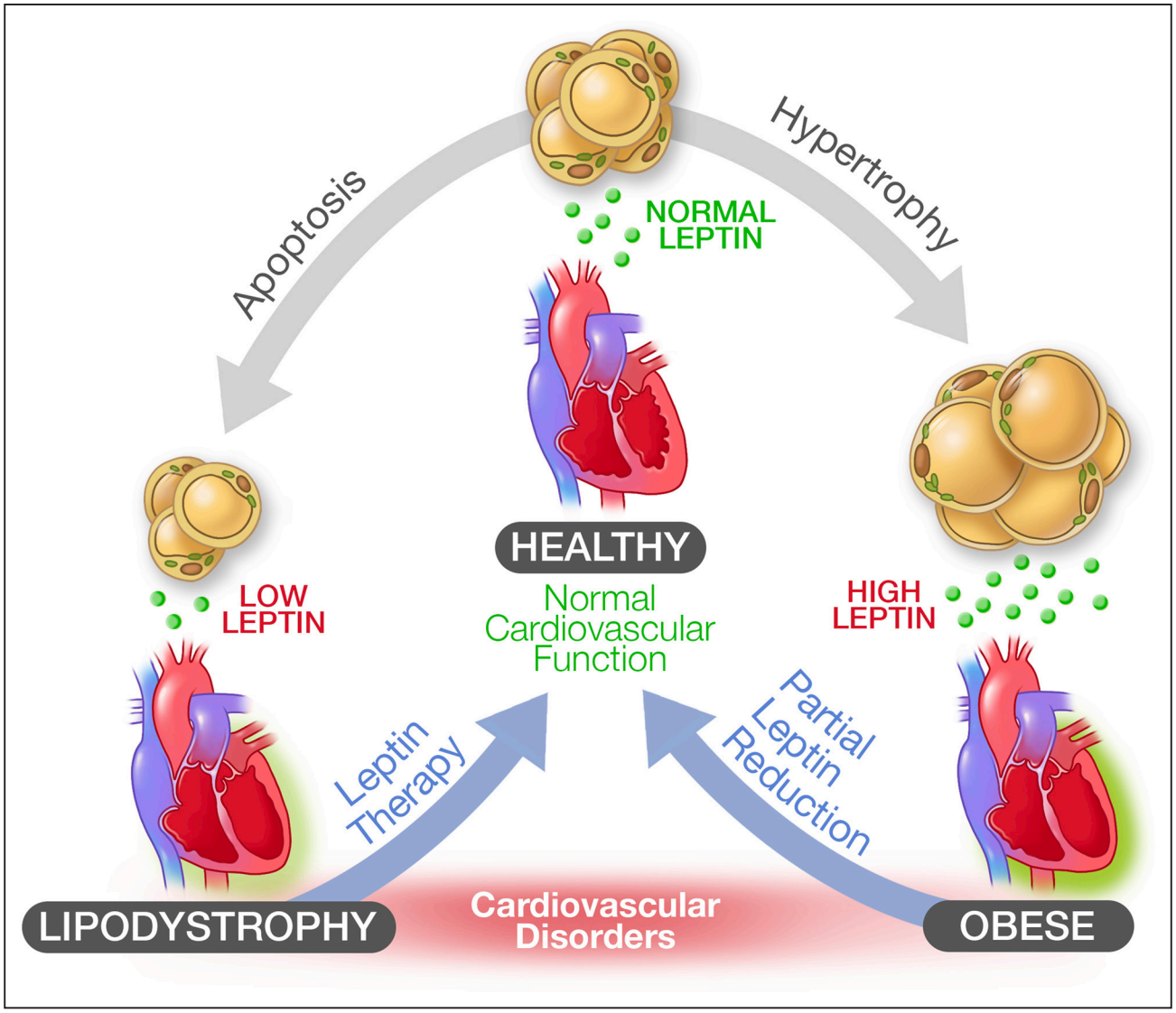

Figure 3. The relationship between the circulating levels of leptin and cardiovascular dysfunction.
For proper cardiovascular function, circulating leptin levels must be maintained within a narrow physiological range. Under conditions of lipodystrophy, caused by widespread adipose tissue apoptosis or an inability to properly develop adipose tissue, extremely low levels of circulating leptin promote cardiovascular disorders, which can be reversed by leptin therapy. Under conditions of diet-induced obesity, hyperleptinemia is a driving force for cardiovascular dysfunction due to leptin resistance, which can be restored by reducing circulating leptin levels (partial leptin reduction).

is more."[90] This provides an alternative strategy to treat obesity-associated cardiovascular disorders; essentially by lowering the circulating levels of leptin.

ADIPONECTIN

Adiponectin was first described in 1995,[35] around the same time as the initial description of leptin. Adiponectin is produced and predominately secreted by adipose tissue.[35] The adipokine exerts its beneficial effects on multiple tissues, including the heart, liver,[93] pancreatic β-cells,[94] the brain,[95] bone,[96] kidneys,[97] blood vessels,[98,99] and immune cells.[99] Adiponectin in circulation exists in 3 major oligomeric multimers: a low-molecular weight trimer, a medium molecular weight hexamer, and a high molecular weight (HMW) multimer.[100] HMW adiponectin represents the biologically most active form of adiponectin. In contrast to other adipokines, the circulating levels of adiponectin are inversely proportional to total fat mass.[101] This is particularly striking for the relationship between adiponectin and leptin. Under almost all physiological conditions, these 2 adipokines are regulated in an opposite manner. High leptin generally reflects low adiponectin, and vice versa, low leptin reflects high adiponectin. For instance, obese individuals with high circulating levels of leptin, display lower levels of adiponectin. Furthermore, adiponectin secretion is predominantly determined by the quality of adipose tissue, rather than the amount of adipose tissue. Despite comparable levels of adipose tissue, metabolically healthy obesity (healthy) individuals display

higher levels of circulating adiponectin, when compared with metabolically abnormal obesity (unhealthy) individuals.[102] Whether high adiponectin levels can account for all of the beneficial metabolic characteristics of metabolically healthy obesity individuals is currently not clear. However, murine models that overexpress adiponectin, do indeed exhibit a massive metabolically healthy obesity phenotype.[31]

As a pleiotropic hormone, adiponectin very robustly enhances insulin sensitivity, in addition to promoting anti-inflammatory and antifibrotic activity.[103,104] Congenital deletion of adiponectin impairs glucose tolerance and reduces insulin sensitivity.[105,106] This phenotype has been fully confirmed and expanded through the use of a doxycycline inducible deletion of adiponectin exclusively in mature adipose tissue.[107] Conversely, overexpression of adiponectin in a transgenic setting, greatly enhances insulin sensitivity, despite massive obesity.[31] Furthermore, increasing the levels of adiponectin through exogenous administration also effectively enhances insulin sensitivity.[108] The beneficial effects of adiponectin are dependent on the protein binding to its receptors, AdipoR1 and AdipoR2. Deletion of AdipoR1 or AdipoR2 abolishes the beneficial effects of adiponectin.[109] Consistent with this observation, overexpression of AdipoR1 and AdipoR2 restores the beneficial effects of adiponectin in several tissues.[110] Of note, an AdipoR1 and AdipoR2 agonist (AdipoRon), ameliorates diabetes in a genetically obese rodent model (*db/db* mice) and prolongs the life-span of *db/db* mice during high-fat diet feeding.[111] Our own studies established that the potent ceramide-reducing effect of adiponectin relies on the ceramidase domain contained within the AdipoR1 and AdipoR2 receptors.[110]

THE PARADOXICAL EFFECT OF ADIPONECTIN ON CARDIOVASCULAR DYSFUNCTION

Given its robust effects on inflammation and fibrosis, we would predict that adiponectin has a protective role against cardiovascular disorders. There is no doubt that low levels of adiponectin are tightly associated with the increased prevalence of obesity-linked cardiovascular disorders, including ischemic heart disease and peripheral artery disease (Figure 2). However, the situation is more complex in the setting of higher circulating adiponectin levels. In some cases, higher circulating levels of adiponectin are associated with a better outcome for cardiovascular events. Conversely in other cases, higher levels of adiponectin are associated with no beneficial effects, or even detrimental effects, such as increasing mortality rate. At times, this is referred to as the adiponectin paradox (Figure 1). This phenomenon was first observed in the context of cardiovascular and kidney disease. It has also been evident in a subset of elderly patients with type 2 diabetes.[112,113]

Given that adiponectin levels are inversely correlated with fat mass, obesity-associated hypoadiponectinemia may serve as a bridge between obesity and cardiovascular disorders. Numerous human studies have provided firm evidence that hypoadiponectinemia is associated with adverse cardiovascular events. For instance, in patients with coronary artery disease, the ratio of HMW adiponectin per total adiponectin is significantly lower, while the trimeric form is significantly higher. Consistent with these observations, weight loss in obese individuals increases the HMW form of adiponectin, while reducing the hexameric and trimeric forms.[114] In agreement with clinical data, cell-culture based studies and murine model systems further provide a clear picture that adiponectin, particularly the HMW form, is beneficial for cardiovascular function.

DISSECTING THE PARADOXICAL EFFECT OF ADIPONECTIN

To delineate the mechanisms that underlie the paradoxical effects of adiponectin in cardiovascular mortality, we turn our attention to the source of circulating adiponectin, in the context of cardiovascular dysfunction. In theory, the circulating levels of adiponectin are determined by the intricate balance between production and clearance. Adipose tissue is the predominant source for circulating adiponectin. Cardiomyocytes can also produce small amounts of adiponectin, which exert local autocrine or paracrine effects, however, do not significantly contribute to circulating levels.[115] As such, adipose tissue is the primary source of adiponectin released into circulation. Beyond its origin, the quality, not quantity, of adipose tissue determines the rate of adiponectin release. In patients with severe cardiovascular disorders, the quality of adipose tissue is largely compromised, as reflected by increased adipose tissue inflammation.[116] Therefore, increased levels of adiponectin may be attributed to delayed clearance, rather than production. Adiponectin is rapidly cleared with a half-life of ≈75 minutes under normal physiological conditions, primarily by the liver[117] and to a much lower extend, the kidney. High adiponectin levels are detected during chronic liver disease, and further, correlate with inflammation and liver damage; reflecting a delayed clearance rate.[118] Additionally, diet-induced obese mice, or *db/db* mice, exhibit a much slower rate of adiponectin clearance. This points to a liver-mediated delay in adiponectin clearance as the primary cause for the higher levels of adiponectin evident in patients with cardiovascular disorders. Consistent with this observation, the adiponectin paradox frequently occurs in patients with both cardiovascular disorders and other metabolic disorders, such as liver or kidney disease. Beyond synthesis and clearance, other variables, such as race, sex, age, smoking, body mass index (BMI), and drug regimen history, can determine the levels of adiponectin in circulation. The circulating levels of adiponectin are increased with age; a phenomenon that is more

pronounced in men than in women.[119] Moreover, BMI is a strong correlate that determines adiponectin levels, that is, subjects with a lower BMI tend to exhibit higher circulating levels of adiponectin. Furthermore, certain pharmacological interventions that directly target adipose tissue, have been shown to regulate adiponectin secretion. For instance, the PPARγ agonist rosiglitazone, a classical drug used to treat type 2 diabetic patients, increases adiponectin secretion.[120] Furthermore, cardiomyocytes may also contribute to the increase in the rate of adiponectin production. However, the physiological relevance of the latter remains to be evaluated, through use of a murine model of cardiomyocyte-specific elimination of adiponectin. Taken together, these confounding factors all contribute to the increased levels of circulating adiponectin evident in patients with cardiovascular dysfunction. Based on these observations, the elevated levels of adiponectin may be a secondary consequence, rather than a primary driver of cardiovascular dysfunction.

Another unanswered question is whether the high levels of adiponectin, in the context of the adiponectin paradox, reflect fully functional material? In some population-based studies, that is, in elderly individuals with a cardiovascular disorder, there is a significant correlation between the total levels of adiponectin with a higher mortality rate. The correlation between HMW adiponectin and increased mortality is, however, less straight-forward.[121,122] Given HMW adiponectin accounts for much of the protective effects in the heart, this may raise the issue as to whether adiponectin is in a functional configuration in these settings. So far, no attempts have been made to directly verify this. Utilizing more functional readouts to confirm the role of HMW adiponectin in the heart, in the context of the adiponectin paradox, are required to fully understand the reasons for the disproportionally high levels of the protein in circulation.

As the physiological role of adiponectin is well preserved from mouse to human, observations made in the context of mouse models generally translate to significant implications for clinical studies. The adiponectin paradox is primarily observed in human prospective studies. Surprisingly, we have not observed this paradox in any rodent models. The presence of high levels of adiponectin in individuals with a severe cardiovascular disorder may be merely a compensatory response in attempt to restore heart function; rather than reflecting a detrimental role to accelerate the disease progression. Currently, no attempt has been made to reduce adiponectin levels in patients with cardiovascular disorders, to support the idea that adiponectin directly contributes to disease progression on the basis of its upregulation. Rodent data strongly argues for the beneficial aspects of adiponectin. The inducible deletion of adiponectin in adult mice produces a strong phenotype; this includes profound insulin resistance and inflammation, severely impaired glucose tolerance and delayed lipid clearance.[107] While high adiponectin levels, on the contrary, as achieved by transgenic overexpression or exogenous administration, produces substantial improvement in cardiovascular function.[123] Furthermore, activation of the adiponectin receptors (AdipoR1 and AdipoR2), by using AdipoRon, alleviates the diabetic phenotype in genetically obese rodent models, that is, in the *db/db* mouse; a mouse model that exhibits severe cardiovascular dysfunction. At the cellular level, in vitro studies using cells or primary cardiomyocytes isolated from heart tissues of fetal or adult rodents, have been used to show a protective effect of adiponectin on cardiomyocyte function.

USING LEPTIN AND ADIPONECTIN AS A STRATEGY TO PREVENT OR TREAT CARDIOVASCULAR DYSFUNCTION

Proper leptin signaling is necessary and indispensable to maintain optimal performance of the heart (Figure 2). Leptin insufficiency, primarily observed in lipodystrophy and leptin-deficient mouse models, is associated with cardiovascular disorders.[75,124–126] In contrast, hyperleptinemia, frequently observed in diet-induced obesity, also results in cardiovascular disorders and increased mortality rates. As such, targeting a leptin-based therapy to treat cardiovascular disorders, should focus on the circulating levels of leptin. In the setting of complete leptin insufficiency, leptin therapy (by elevating leptin concentrations to physiological levels) is adequate to prevent or reverse cardiovascular disorders (Figure 3). Successful application of metreleptin (a recombinant form of leptin) to treat patients with lipodystrophy has been well established. More specifically, leptin therapy in these lipodystrophic individuals very effectively normalizes glucose tolerance and insulin sensitivity, to improve liver and heart function.[127] However, in the context of hyperleptinemia, leptin therapy is largely ineffective. Rather, a partial leptin reduction strategy, by reducing the circulating levels of leptin to achieve a normal systemic range, shows great promise in treating obesity and its associated cardiovascular disorders (Figure 3). Of note in this context, this approach does not require a sophisticated titration to normalize leptin levels. Based on our experience in the area of metabolism, we identified that there is a wide therapeutic range available for leptin neutralization therapy. Any significant reductions in leptin trigger beneficial effects, that is, leptin levels can be very significantly lowered, but the benefits of this reduction are still preserved.

PARTIAL LEPTIN REDUCTION: A NOVEL STRATEGY FOR THE TREATMENT OF HYPERLEPTINEMIA-ASSOCIATED CARDIOVASCULAR DYSFUNCTION

Recently, we demonstrated that hyperleptinemia per se is sufficient to promote leptin resistance. High leptin

levels serve as a driving force for obesity and its associated metabolic disorders. This offered the possibility that reducing leptin levels in circulation lends itself as an effective strategy to treat obesity and its metabolic consequences.[90] We have already achieved this, essentially by using genetic mouse models, as well as through leptin neutralizing antibodies. Partial leptin reduction restores the physiological role of leptin in reducing food intake and enhancing energy expenditure, which leads to significant weight loss and antidiabetic effects. Based on these findings, we propose that partial leptin reduction will also alleviate the pathogenesis of cardiovascular dysfunction, to effectively improve the outcome of a cardiovascular event.

The effectiveness of partial leptin reduction, in the context of hyperleptinemia, has been indirectly supported by many observations. Lifestyle alterations and pharmacological interventions that demonstrate cardiovascular improvement are associated with a partial reduction in the circulating levels of leptin. For instance, long-term caloric restriction preserves cardiac contractile function, to improve cardiomyocyte function and reduce cardiac remodeling.[128,129] Caloric restriction also effectively lowers the circulating levels of leptin.[130,131] High-intensity training has also been shown to cause partial leptin reduction, concomitant with improved cardiovascular function.[132] From a pharmalogical perspective, the glucagon-like peptide-1 analog, liraglutide, greatly reduces cardiovascular events and mortality rate; this is associated with reduced levels of leptin.[133] Moreover, inhibitors targeting the SGLT-2 (sodium-glucose-linked transporter-2), have emerged as one of the most powerful classes of cardiovascular drugs in recent years.[134] However, little is known about the underlying mechanisms that drive their cardiovascular benefits. Reduced levels of leptin, in the context of SGLT-2 inhibition, could be one of the highly likely mechanisms underlying this phenomenon.[135] Hyperleptinemia results in sodium retention and plasma volume expansion; this can activate cardiac and renal inflammation and fibrosis. Furthermore, leptin-mediated neuro-hormonal activation appears to increase the expression of SGLT-2 in the renal tubule.[136] Other potent cardiovascular interventions, such as the angiotensin-converting enzyme inhibitor perindopril,[137] or metformin, or statins, have direct effects on adipocytes, specifically on white adipose tissue, to decrease leptin expression.[138,139] Finally, CB1 (cannabinoid receptor 1) antagonists have also been used as an additional strategy to lower the circulating levels of leptin.[140,141] Collectively, these known effects of leptin correlate well with cardiovascular benefits, suggesting the possibility to directly target leptin reduction for the treatment of cardiovascular disorders. We therefore propose that reducing the circulating levels of leptin, in the context of hyperleptinemia, can directly lead to cardiovascular improvement. Leptin neutralizing antibodies that effectively lower the circulating levels of leptin,[91] display great promise in inducing weight loss, in addition to exerting antifibrotic and insulin sensitizing effects. To date, however, the effects of such antibody-based approaches on the cardiovascular system are still awaiting further investigation.

ADIPONECTIN THERAPY IN THE PREVENTION OF CARDIOVASCULAR DYSFUNCTION

In individuals that harbor lower circulating levels of adiponectin, identifying means to elevate adiponectin levels to a physiological range, still holds great promise for the treatment of cardiovascular dysfunction. A subset of approved pharmacological interventions that display beneficial effects on cardiovascular disorders, are also associated with increased circulating levels of adiponectin. For example, the use of PPARγ agonists results in a robust increase in adiponectin levels.[142] As an alternative means, rather than increasing the circulating levels of adiponectin, enhancing adiponectin signaling could also serve as an additional strategy to treat cardiovascular disorders. The identification of a small molecule agonist of the adiponectin receptors AdipoR1 and AdipoR2 (referred to as AdipoRon), has generated much interest in the identification of additional ligands targeted towards improvements in cardiovascular disorder. More specifically, several rodent models that enhance adiponectin receptor signaling through AdipoRon, have provided proof-of-principle that this approach may constitute an effective promising therapy to treat cardiovascular dysfunction.[143] As an additional binding partner, T-cadherin (that also binds to adiponectin) has also garnered attention in the treatment of cardiovascular disorder,[144] and as such, some aspects of the cardioprotective effects that adiponectin elicits may be mediated through this additional receptor.[145] In light of this, the adiponectin/T-cadherin complex has been shown to provide cardiovascular protection by enhancing exosomal production and release; secreting cell-toxic products from specific cell types, that is, cells within the vasculature. In this respect, future studies in the area of T-cadherin signaling as a therapeutic intervention to treat cardiovascular disorders should prove illuminating.

INCREASING THE ADIPONECTIN/LEPTIN RATIO: AN EMERGING STRATEGY TO TREAT CARDIOVASCULAR DYSFUNCTION

Instead of individually targeting adiponectin and leptin, interventions that directly act on both axis separately, to increase the adiponectin to leptin ratio have recently garnered attention.[146–149] In chow-fed mice, the average adiponectin levels are approximately 15 to 20 μg/mL,

while the circulating leptin levels are approximately 5 to 10 ng/mL; as such, the calculated ratio is between 1 and 4;[91] a ratio positively associated with metabolic health and reduced cardiovascular disorder. However, in diet-induced obese mice, this ratio is greatly reduced, as a result of unhealthy adipose tissue expansion, leading to dysfunctional adipose tissue and cardiovascular disorders, which are characterized by increased systemic inflammation and tissue fibrosis.[20,21,150] In diet-induced obese mice, adiponectin levels drop to 10-15 μg/mL, and leptin levels are greatly increased to 50-150 ng/mL, and thus the calculated ratio is much lower than one.[91] In clinical settings, the ratio of adiponectin to leptin is a more predictive and reliable biomarker for several metabolic disorders, such as insulin resistance, type 2 diabetes, hypertension, and cardiovascular disorders.[151] Therefore, in obese patients with cardiovascular dysfunction, an ideal treatment would be to combine the beneficial effects of both adiponectin therapy and partial leptin reduction. Weight loss is associated with a significantly elevated ratio, as progressive weight loss elevates adiponectin levels and reduces leptin levels.[152] Thus, pharmacological interventions and bariatric surgery that induce substantial weight loss, could serve as a strategy to elevate the ratio.[153–156] However, it is still unclear whether the cardiovascular beneficial effects of weight loss are directly derived from an elevated ratio of adiponectin to leptin. Further experiments are definitely warranted to confirm this causing effect.

Independent of significant weight loss, simpler treatments that aim to simultaneously elevate adiponectin and reduce leptin levels are still under development. The recently developed leptin neutralizing antibody, together with PPARγ agonists that lead to long-lasting adiponectin increases, may be an excellent combination therapy to achieve an elevated ratio. The efficacy and efficiency of this combination therapy in reversing cardiovascular disorders is yet to be determined. Based on the positive outcomes of monotherapy of leptin neutralization, a much better outcome in treating obesity-associated cardiovascular disorders could be expected. In addition, the existence of multiple mouse models, including doxycycline inducible leptin transgenic mice, adiponectin overexpression mice, inducible leptin and adiponectin KO (knockout) mice with tissue specific Cre expression,[157] will allow us to better examine the cause and effect relationship of the ratio of adiponectin to leptin in cardiovascular disorders.

CONCLUSIONS AND PERSPECTIVE

The pathogenesis of cardiovascular dysfunction is highly complex. Two of the most widely studied adipokines, adiponectin and leptin, are important players in determining cardiovascular disorder progression and outcome. Essentially, both adipokines are required for proper cardiovascular function. Impaired leptin or adiponectin signaling, due to lipodystrophy or genetic mutations, results in an adverse outcome of cardiovascular dysfunction. On the contrary, an oversupply of leptin or adiponectin in circulation, can directly exert a negative cardiovascular impact; whereas the paradoxical increase of adiponectin in this context, is likely a reflection of a compensatory response. A combined approach aimed at restoring normal physiological levels of both adipokines is highly likely to elicit a positive cardiovascular outcome. Here, we propose that an increased ratio of adiponectin to leptin can emerge as a highly promising and aspirational therapeutic goal.

ARTICLE INFORMATION

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