Chapter

# Obesity-Related Myocardiopathy

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## Abstract

Cardiovascular disease in populations with obesity is a major concern because of it is epidemic proportion. Obesity leads to the development of cardiomyopathy directly via inflammatory mediators and indirectly by obesity-induced hypertension, diabetes, and coronary artery diseases. Metabolic disturbances such as increased free fatty acid levels, insulin resistance, elevated levels of adipokines, myocardial remodeling, activation of the sympathetic nervous and renin-angiotensin-aldosterone systems, and small-vessel disease are the most important mechanisms in the development of obesity cardiomyopathy. The myocardial changes related with obesity are increasingly recognized, and they are independent of classic risk factors as hypertension, coronary artery disease, and obstructive sleep apnea. There is a wide range of evidence: the association between heart failure and obesity shown in epidemiologic studies; the confirmation of the association of adiposity with left ventricular dysfunction, independent of hypertension, coronary artery disease, and other heart diseases; and experimental evidence of functional and structural changes in the myocardium in response to increased adiposity support the existence of a cardiomyopathy related to obesity.

**Keywords:** heart failure, obesity, adipokines, myocardiopathy

## 1. Introduction

During the past half-century, the advances in the prevention, diagnosis, and management of cardiovascular disease (CVD) have been spectacular. The cardiovascular-related deaths have declined by about two-thirds in industrialized nations [1].

Heart failure is characterized by an increased rate of cell death, which has been attributed to a variety of conditions: oxidative stress; abnormal elevations in circulating neurohormones; toxins, such as alcohol or cancer chemotherapeutic drugs; excessive adrenergic activity; inflammation; and infiltrative processes. Apoptosis is a highly regulated type of cell death that normally increases with aging. It has been suggested that, over time, the resulting deletion of myocytes leads to heart failure [2, 3].

The metabolic demand is increased in obesity; this is due to different factors as increasing blood volume, greater adipose tissue and lean mass, and as such, increased preload to the heart. In addition, in obese patients there are vascular alterations impacting arterial stiffness, and resistance increases afterload to the heart. In adults with obesity, both eccentric and concentric hypertrophies have been noted and are impacted by the duration and the degree of the obesity [4, 5].

## 2. Regional adiposity and cardiovascular risk

While the cardiovascular risk is linked to the adipose tissue quantity, recent data indicate that differences in fat tissue quality, which can be examined directly by noninvasive computed tomography radiodensity attenuation imaging or by immunohistochemistry, are closely linked to insulin resistance, cardiometabolic risk, and all-cause mortality, independent of total fat volume. These data demonstrate, independent of body mass index, that abnormalities at the adipose tissue level may be key factors that regulate systemic metabolism and drive cardiometabolic disease. These qualitative abnormalities in fat are a growing area of research interest that have been recently termed sick fat or adiposopathy and may in part explain the clinical observation of metabolically healthy obesity. The interindividual variability in adipose tissue "quality" may be related, in part, to differences in lifestyle, as physical activity has effects on adipose tissue physiology and cardiometabolic risk. While animal models of obesity tend to generate fairly uniform phenotypes, the degree of adipose tissue dysfunction in obese humans exhibits significant heterogeneity with lower degrees of adiposopathy being associated with more favorable systemic metabolic profiles and vascular function.

## 3. Adipokines, myokines, and cardiovascular disease

It is recognized that obesity contributes to cardiovascular and metabolic disorders through alterations in the levels of adipocyte-derived cytokines that are named adipokines.

The functions of adipose tissue are as energy storage and as secretory tissue producing a variety of bioactive substances, including leptin, tumor necrosis factor alpha (TNFα), plasminogen activator inhibitor type 1, and adiponectin [6–9]. These bioactive molecules are generally referred to as adipokines, and several are involved in the pathophysiology of various obesity-linked disorders.

## 4. Leptin

Leptin is an adipose tissue-specific-secreted hormone and is highly expressed by adipocytes; this adipokine is encoded by the ob gene, which was identified in genetically obese ob/ob mice through positional cloning. The circulating leptin levels increase in parallel to adipose tissue mass. Leptin exerts important metabolic actions by suppressing appetite and increasing energy expenditure. Many lines of evidence suggest that hyperleptinemia contributes to cardiovascular complications. Leptin has pro-inflammatory actions in many immune cell types including monocytes/macrophage, neutrophils, NK cells, and T cells [10–17].

## 5. Adiponectin

Adiponectin is abundantly present in human plasma at a range between 3 and 30 μg/mL. It is an adipokine whose mRNA is largely expressed in adipose tissue. Adiponectin multimerizes to form stable higher-order complexes and shares structural homology with the collectin family of proteins.

Lower plasma levels of adiponectin are implicated in the pathogenesis of obesity-related diseases [18–21]. Conversely, plasma adiponectin concentrations

increase following weight loss [22, 23]. In patients with diabetes mellitus, the levels of adiponectin are lower than patients without diabetes matched for age and weight [14]. An inverse correlation has been demonstrated between circulating levels of adiponectin and those as C-reactive protein and interleukin 6 [24–27].

Adiponectin appears to protect against the development of various vascular diseases. In murine experiments, it has been demonstrated that adiponectin has an anti-atherogenic function. In apolipoprotein E-deficient mice, the administration of an adenovirus-expressing adiponectin reduces atherosclerotic lesion size [28]. In apolipoprotein E-deficient mice, the adiponectin deficit leads to an increase in vascular lesion area [29]. Adiponectin knockout mice also develop increased neointimal thickness and display increased vascular smooth muscle cell proliferation following acute arterial injury, whereas overexpression of adiponectin inhibits neointimal lesion formation in wild-type mice [30].

Experimental studies have found that adiponectin exerts beneficial actions on the heart under pathological conditions. Adiponectin-deficient mice develop severe cardiac hypertrophy, and there is increased mortality in response to pressure overload because of transverse aortic constriction [31, 32].

## 6. Interleukin 6

Interleukin 6 (IL-6) is known to be secreted by several tissues; it is a pleiotropic cytokine with complex roles in metabolic and cardiovascular disease. IL-6 also can act in a local fashion. However, adipose tissue is a major source of this protein, capable of producing high levels of this protein in the blood. It has been estimated that as much as one-third of total circulating IL-6 originates from adipose tissue. Therefore, IL-6 can be considered an adipokine with endocrine actions.

IL-6-induced cell signaling is typically classified as either classic or trans-signaling, and it can lead to different cell responses. In the classic signaling way, the target cells are stimulated by IL-6 stimulates via a membrane-bound IL-6 receptor (IL6R), which upon ligand binding forms a complex with the signaling receptor protein gp130. Essentially all cells exhibit gp130 on the cell surface, whereas few cell types express membrane-bound IL6R. While the cells that only express gp130 are not responsive to IL-6 alone, they can be stimulated, via trans-signaling, by a complex of IL-6 bound to a naturally occurring soluble form of IL6R (sIL6R), markedly expanding the spectrum of IL-6 actions and target cells.

## 7. Resistin

Resistin is highly expressed by mature adipocytes in rodents. This adipokine is a secreted protein that was initially suggested to be a major link between insulin resistance and obesity. Circulating resistin levels are increased in diabetic and obese mice, and the important role of resistin in metabolic dysfunction associated with obesity through pleiotropic effects on insulin sensitivity and glucose metabolism has been suggested in several loss- and gain-of-function studies in mice .

## 8. Myokines

Myokines have been defined as cytokines and proteins produced and released by myocytes under the action of contractile activity. They exert an autocrine,

paracrine, or endocrine effect. Their receptors were found in the muscle, fat, liver, pancreas, bone tissue, heart, brain, and immune cells [33, 34].

Although the endocrine function of adipose tissue has long been recognized, most of the factors produced are pro-inflammatory and harmful in the setting of obesity-induced metabolic disorders and cardiovascular disease. In this regard, adiponectin is relatively unique as an adipokine because it is expressed at highest levels in lean, healthy individuals.

Candidate cDNAs that encode secreted proteins and are differentially regulated in the muscle of the MyoMouse model are then used to construct adenoviral vectors for further testing in animal models of disease. One such factor, follistatin-like 1 (Fstl1), was identified in this type of screen and shown to have cardiovascular-protective properties. Fstl1, also referred to as TSC36, is an extracellular glycoprotein that has been grouped into the follistatin family of proteins [35].

The main myokines studied to date are myostatin, decorin, irisin, myonectin, interleukin-6 (IL-6), interleukin-8 (IL-8), interleukin-15 (IL-15), follistatin, fibroblast growth factor 21 (FGF21), bone morphogenetic protein (BMP), and brain-derived neurotrophic factor (BDNF). Other possible factors have been detected in the skeletal muscle, but their functions, as well as their presence in the circulation, are largely unknown: musclin and nonneuronal acetylcholine.

## 9. Myostatin

Also called growth differentiation factor 8 (GDF-8), it is a member of the transforming growth factor-β (TGF-β) family, expressed in developing and adult muscular tissue. It is one of the first described myokines.

Its main function is the negative regulation of the muscle mass, which means high level of myostatin and less muscle mass. It plays a role in stopping myoblast proliferation and suppressing satellite cell activation, inducing muscle atrophy. In addition, it influences the differentiation of muscle fibers by types (fast and slow) and the arrangement of muscle glucose as well as the muscle-adipose tissue cross-talking [36–40].

## 10. Irisin

Discovered in 2012 as a transmembrane protein, FNDC5 has a cleaved soluble form, irisin, that it is released into circulation during the proteolytic process after acute exercising of skeletal muscles. It increases the energetic and oxidative metabolism of the muscle by activating genes related to these processes. It has a high level during myogenesis and induces glucose uptake improving glucose homeostasis, inhibiting lipid accumulation, and reducing body weight [41, 42]. Irisin has been studied especially in relation to obesity but also with myopathies such as muscular dystrophy. In these latter studies, injection of irisin induced muscle hypertrophy, improving muscle strength and reducing necrosis and development of connective tissue in a murine model [42].

## 11. Myonectin

Myonectin is a protein belonging to the C1q/TNF-related protein (CTRP) family, and it is found mainly in the muscle, less in circulation, being especially related to nutritional metabolism. Thus, the expression of myonectin is stimulated

by exercise and nutrients and is supposed to induce nutrient uptake and storage in other tissues, such as adipose tissue, causing a flux of glucose or fatty acids [42, 43].

## 12. Mechanism of myocardiopathy in obesity

Insulin resistance, adiposity, and adipokines have been implicated in the development of abnormal myocardial mechanics in adults with obesity and type 2 diabetes. Adiposopathy in obese individuals is ultimately the consequence of a dysfunctional remodeling of the adipose tissue. Therefore, for understanding how obesity contributes to cardiovascular disease, it is primordial to know how both quantitative and qualitative effects of this adipose tissue remodeling contribute to that.

## 13. Adipose tissue expansion

In response to an excessive caloric intake, the mechanisms by which adipose depots expand represent an important determinant of the risk of cardiovascular disease and metabolic dysfunction. This expansion is mediated by two ways: an enlargement of adipocyte size (hypertrophy) and/or an increase in adipocyte numbers (hyperplasia).

Adipocyte hypertrophy typically leads to lipid-laden, dysfunctional adipocytes that undergo cell death and contribute to adipose tissue inflammation, dysfunction, and associated pathologies; in contrast it has been classically accepted that hyperplasia allows a "healthy" expansion of the adipose tissue, since it is mediated by the formation of functional adipocytes from progenitor cells (adipogenesis).

## 14. Immune cell infiltration

In most cases chronic excessive caloric intake eventually leads to adipocyte dysfunction, regardless of the mechanisms of adipose tissue expansion, and this is paralleled by qualitative and quantitative changes in the composition of adipose tissue at cellular level. Immune cells are of great relevance in this regard. Low-grade chronic inflammation is a major hallmark of adipose tissue in obesity, and it is now known that almost every immune cell type can be found in the adipose tissue. Total numbers of B cells, T cells, neutrophils, macrophages, and mast cells are increased in visceral adipose tissue of obese individuals. In contrast, the number of eosinophils and specific subsets of T cells—T-helper type 2 (Th2) cells and regulatory T (Treg) cells—are decreased or remained static in the adipose tissue of obese individuals [36].

Macrophages are the most abundant immune cell in the adipose tissue of obese individuals, and their recruitment and proliferation upon high-calorie feeding is generally associated with adipose tissue inflammation and insulin resistance [44–47].

## 15. Impaired vascular structure and function

Several studies in humans and animal models have shown that obesity induces capillary rarefaction in adipose tissue, and this has been associated with metabolic dysfunction. It is widely a reduced adipose tissue; capillarization is present in obesity, and this reduced blood supply may limit nutrient delivery and contribute to adipocyte dysfunction and insulin resistance.

Evidence of a causal role of adipose tissue vascularization in obesity-associated metabolic dysfunction have been shown in recent studies with genetically engineered mice. Experiments demonstrated that an increased VEGF-mediated angiogenesis in adipose tissue can attenuate some of the metabolic effects of diet-induced obesity, such as insulin resistance and hepatic steatosis in mice overexpressing vascular endothelial growth factor A (VEGF-A) in adipocytes. Conversely, adipocyte-restricted deletion of VEGF-A results in diminished adipose tissue vascularization, which leads to increased adipose tissue inflammation and systemic metabolic dysfunction further supporting the noxious effects of reduced adipose tissue vascularity in obesity [48–51].

## 16. Adipose tissue fibrosis

Within the adipose tissue of lean organisms, adipocytes are surrounded by extracellular matrix that provides mechanical support and participates in cell signaling. There is a general increase in the synthesis of several extracellular matrix components with the development of obesity, in particular collagen VI, which leads to adipose tissue fibrosis and is associated with impaired metabolic function in mice. Adipose tissue fibrosis is increased in both subcutaneous and visceral depots in obesity. Obesity-induced adipose tissue fibrosis is due, at least in part, to hypoxia-induced upregulation of hypoxia-inducible factor 1α (HIF1α). Interestingly, HIF1α activation does not contribute to an angiogenic response in this context, but instead promotes adipose tissue fibrosis [52].

## 17. Conclusions

An increasing evidence supports the evolving concept that quality, quantity, and location of adipose tissue are critical factors in shaping cardiometabolic phenotypes in obese individuals. The specific pathogenic mechanisms and their relative contributions remain incompletely understood. Adipose tissue communicates with remote organs, including the heart and vasculature, through the release of various adipokines. While some adipokines have been highly studied and have shown to be causally linked to various disease processes, new adipokine candidates continue to be discovered and elucidated. In murine models and many human individuals, obesity leads to adipose tissue dysfunction; this dysfunction is termed adiposopathy, particularly in visceral fat depots, which is mediated by dysfunctional tissue remodeling that involves adipocyte hypertrophy, increased fibrosis exacerbated inflammation, and impaired vascular function and structure. This ultimately creates a chronic, low-grade systemic inflammatory reaction mediated by an imbalance in adipokine levels which contributes to the initiation and progression of metabolic and cardiovascular complications. As our understanding of adipokines and obesity-induced adiposopathy increases, the major challenge will reside in translating this information into new prognostic and therapeutic approaches to limit cardiovascular risk in obese individuals. Considering that a third of the world's population is currently overweight or obese and this proportion is expected to increase in the coming decades, studies of adipokine biology should provide a better understanding of the pathogenesis of cardiovascular disease.

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