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The Insight into the Role of Leptin and Its Receptor in Heart Failure with Preserved Ejection Fraction

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ABSTRACT

Heart failure with preserved ejection fraction (HFpEF) is a complex clinical syndrome with a multifactorial pathogenesis. Leptin, a hormone produced by adipose tissue, plays a key role in regulating energy balance, metabolism, and inflammatory processes. Its impact on the cardiovascular system is dualistic: on one hand, leptin can contribute to the development of HFpEF by promoting inflammation and metabolic dysfunction; on the other hand, it may exert protective effects by reducing body weight and enhancing metabolic functions. This literature review examines current data on leptin's role in HFpEF, exploring both its detrimental and beneficial effects. The objective is to elucidate the mechanisms through which leptin influences the onset and progression of HFpEF, potentially guiding the development of more targeted therapeutic strategies.

AIM

The aim of this review is to examine the role of leptin in the pathogenesis of heart failure with

preserved ejection fraction (HFpEF). The analysis includes both the potential detrimental and protective effects of leptin on the cardiovascular system. We aim to elucidate how leptin influences the development and progression of HFpEF, which may inform the development of more targeted therapeutic strategies.

MATERIAL AND METHODS

For this review, we used the literature available in PubMed. The keywords used included "Leptin", "Heart failure with preserved ejection fraction", "inflammation", "obesity" "leptin receptor", "cardiac fibrosis", "diastolic dysfunction".

CONCLUSIONS

In conclusion, leptin by its action can contribute to the development of HFpEF in various mechanisms. On the other hand, it can have a protective effect on the heart muscle. Hyperleptinemia can cause tissue resistance to leptin, from which it could be concluded that the lack of response to leptin actually leads to HFpEF. Additional studies are needed to confirm or correct these assumptions.

KEYWORDS: leptin, Heart failure with preserved ejection fraction, inflammation, obesity, leptin receptor, diastolic dysfunction

CURRENT STATE OF KNOWLEDGE

The pathogenesis of HFpEF is complex and involves several mechanisms. One of the primary mechanisms involved in HFpEF is the development of diastolic dysfunction, which is characterized by impaired relaxation and increased stiffness of the heart muscle. (1), (2), (3). This results in an impaired ability of the heart to fill with blood properly, leading to elevated pressures within the heart and lungs, and ultimately leading to symptoms of heart failure. However, it has become clear that HFpEF is a heterogeneous condition with multiple underlying causes. There are several factors that can contribute to the development of diastolic dysfunction and subsequent HFpEF. These include

1. **Age-related changes**: As individuals age, there is a natural decline in the function of the heart and blood vessels, leading to increased stiffness and decreased ability to relax (4) (5)
2. **Obesity**: Obesity is a significant risk factor for HFpEF. Adipose tissue produces inflammatory cytokines and adipokines, which can contribute to the development of systemic inflammation and endothelial dysfunction, leading to impaired diastolic function. (2), (6), (7), (8), (4)
3. **Diabetes**: Diabetes is another significant risk factor for HFpEF. Chronic hyperglycemia can lead to the production of advanced glycation end products (AGEs), which can cause endothelial dysfunction and contribute to the development of diastolic dysfunction. (9), (10), (11), (4)
4. **Hypertension**: Chronic hypertension can lead to remodeling of the heart and blood vessels, in increased stiffness and impaired relaxation. (4), (12)
5. **Chronic kidney disease**: Chronic kidney disease is a significant risk factor for HFpEF. This is thought to be due to the development of systemic inflammation and endothelial dysfunction, as well as impaired sodium and water handling by the kidneys, leading to volume overload and increased cardiac workload (13), (12), (4).
6. Inducible nitric oxide synthase (iNOS), overexpression Unfolded Protein Response, endoplasmic reticulum stress, play a significant role in the pathogenesis of HFpEF. (14).

Leptin is a hormone produced mainly by adipose (fat) tissue in the body (15). Its primary role is to regulate appetite and energy expenditure by signaling to the brain when the body has enough energy stores (in the form of fat) and when it needs to reduce food intake or increase energy expenditure. Leptin plays an important role in the regulation of energy balance, glucose metabolism, and inflammation, all of which are implicated in the pathogenesis of cardiometabolic disorders such as obesity, type 2 diabetes, and cardiovascular disease. (16) (17), (18), (19), (17), (20). Leptin was first discovered in 1994 and has since been the subject of extensive research due to its role in obesity and other metabolic disorders (21). Leptin resistance, or reduced responsiveness to leptin signaling, is a hallmark of obesity. Despite high levels of circulating leptin, obese individuals are often unable to suppress their appetite or increase energy expenditure, leading to further weight gain. This suggests that dysregulation of leptin signaling may contribute to the development and maintenance of obesity (22), (23), (24). Leptin has been shown to regulate glucose metabolism by increasing insulin sensitivity and promoting glucose uptake in peripheral tissues. However, in individuals with obesity and insulin resistance, leptin signaling may be impaired, leading to reduced glucose uptake and increased blood glucose levels. This may contribute to the development of type 2 diabetes (17), (25), (26). Leptin has been implicated in the pathogenesis of atherosclerosis, a major contributor to cardiovascular disease. Leptin has been shown to promote inflammation and oxidative stress in the arterial wall, leading to endothelial dysfunction and the development of plaques. Additionally, leptin has been shown to stimulate the sympathetic nervous system, leading to increased heart rate and blood pressure, both of which are risk factors for cardiovascular disease (27), (28), (29) (30), (31). Leptin has been demonstrated to regulate a variety of cardiac and vascular effects, which include angiogenesis, thrombosis, hemodynamics, and cardiac hypertrophy. Leptin signals through the leptin receptor (LEPR). Its expression and function may be influenced by factors such as obesity, myocardial ischemia and reperfusion. (32), (33), (34), Circulating levels of leptin have been found to be increased under various pathological conditions, such as obesity, chronic obstructive pulmonary disease, coronary artery disease and chronic heart failure. (35), (33).

LEPTIN AND HFPEF

Leptin has been shown to have both beneficial and detrimental effects on the cardiovascular system. On one hand, it can increase cardiac contractility and promote angiogenesis (36), (37). On the other hand, it can contribute to the development of inflammation, oxidative stress, and fibrosis, which are all involved in the pathogenesis of HFpEF (38), (39). Leptin signaling is

mediated by its receptor, which is expressed in multiple tissues, including the heart and blood vessels. Activation of the leptin receptor can lead to the activation of multiple signaling pathways, including the JAK-STAT and PI3K-AKT pathways, which can have both pro- and anti-inflammatory effects (40), (40), (29), (20). Studies have shown that the expression of the leptin receptor (LEPR) is upregulated in patients with HfpE. Overall, the role of leptin and its receptor in the pathogenesis of HFpEF is complex and multifactorial. The upregulation of the leptin receptor is observed in patients with HFpEF suggests that targeting this pathway may be a promising therapeutic strategy for this condition. (33) This upregulation is associated with increased cardiac fibrosis and diastolic dysfunction. (35), (33). Future research may focus on developing drugs that can block the binding of leptin to the receptor or reduce the expression of the receptor itself. Additionally, animal studies have shown that the inhibition of the leptin receptor can improve diastolic function and reduce cardiac fibrosis in models of HFpEF (41), (42).

LEPTIN AND RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM (RAAS)

The renin-angiotensin-aldosterone (RAA) system plays an important role in Heart Failure with Preserved Ejection Fraction (HFpEF) by promoting fluid retention, hypertension, and myocardial fibrosis, which contribute to diastolic dysfunction (43). Dysregulation of the RAA system exacerbates the pathological remodeling seen in HFpEF. Leptin negatively impacts the RAA system by enhancing its activation. Elevated leptin levels, often observed in obesity, can stimulate aldosterone secretion and increase angiotensin II activity, worsening the fluid overload, inflammation, and fibrosis characteristic of HFpEF (44). This interplay highlights how leptin can indirectly aggravate HFpEF through its influence on the RAA system. Leptin may increase the secretion of aldosterone through various means mechanisms. One of them is the stimulation of the adrenal glands to produce aldosterone. Other reports indicate that leptin increases the secretion of aldosterone through increasing angiotensin II levels. (45) Leptin can directly regulate the expression of CYP11B2 aldosterone synthase, therefore, elevated leptin levels causes an increase in aldosterone levels (Huby et al., 2015). Aldosterone causes sodium and water retention in the kidneys, which promotes the development of hypertension and increases preload. All this promotes myocardial fibrosis, and later HFpEF (47). Elevated concentrations of leptin, aldosterone, and increased renal sympathetic activity are characteristic of people with hyperleptinaemia. Leptin can also increase the response to angiotensin II, thereby inducing hypertension (48), (44), (49).

EFFECT ON ENDOTHELIUM AND NITRIC OXIDE

It was found that in patients with HFpEF the level of 3-NT in plasma is significantly higher than in other groups, suggesting that the pathogenesis of HFpEF is associated with oxidative/nitrosative stress (50). In HFpEF we observe nitrosative/oxidative stress, endoplasmic reticulum stress (51). Endothelial dysfunction and abnormalities in NO production and action can be observated in HFpEF. They cause increased vascular stiffness, worsening of diastolic function, and reduced exercise capacity, which significantly affect symptoms and prognosis in patients with HFpEF (52). Reduced NO production causes endothelial dysfunction, what can be one of the mechanisms of HFpEF development (53), (54).

Many researchers believe that leptin causes negative effects on the heart and the body as a whole only in a state of hyperleptinemia. Leptin reduces passive vascular wall tension by regulating the sympathetic nervous system and secreting NO by vascular endothelium, thereby maintaining balance. Leptin can act through the JAK2/STAT3 and PI3K/Akt pathways to reduce passive vascular wall tension (40).

On one hand, hyperleptinemia causes resistance to leptin, resulting in a noticeable reduction in NO synthesis by the vascular endothelium . Also pro-inflammatory effect of leptin may reduce NO synthesis On the other hand, leptin can increase NO secretion by the vascular endothelium (53), (55).

LEPTIN, AUTONOMIC SYSTEM AND HYPERTENSION

Hypertension is one of the primary risk factors for HFpEF (56). Chronic high blood pressure leads to increased left ventricular afterload, resulting in myocardial hypertrophy and stiffness. Chronic hypertension increases the pressure load on the heart, leading to left ventricular hypertrophy (LVH). LVH increases the stiffness of the heart walls and impairs its relaxation, which is characteristic of HFpEF (56). In a study on mice, leptin was found to play a key role in the pathomechanism of hypertension in obesity. Decreasing leptin levels, reducing LepR expression or blocking the receptor with specific antibodies resulted in a reduction in blood pressure in mice. At the same time, observations suggest that a similar mechanism works in the human body, although this assumption still needs to be thoroughly investigated (57) . In turn, hypertension, causes hypertrophy of left ventricle, resulting in diastolic dysfunction and heart failure (56). Over time, this impairs the ability of the left ventricle to relax properly during diastole, contributing to diastolic dysfunction, which is the hallmark of HFpEF. Additionally, hypertensive episodes can cause microvascular dysfunction and inflammation, further worsening cardiac remodeling. (56). Leptin receptors are widely distributed in various tissues,

including the heart. Whereas increased plasma leptin levels have been reported in patients with congestive heart failure, systemic alterations induced by obesity can affect cardiac hypertrophy. On the othej hand the direct effects of leptin on cardiac structure and function still remain to be determined (49).

Autonomic dysfunction, characterized by an imbalance between sympathetic and parasympathetic activity, is common in HFpEF. Increased sympathetic activation leads to elevated heart rate, vasoconstriction, and sodium retention, which contribute to hypertension and fluid overload (58). Elevated levels of leptin, aldosterone and neprilysin and an increase in the sympathetic activity of the kidneys were were characteristic of women. (Packer, 2018b). Reduced parasympathetic tone worsens heart rate variability and impairs baroreceptor reflexes, aggravating cardiovascular dysfunction. Together, these factors exacerbate myocardial stress, diastolic dysfunction, and exercise intolerance in HFpEF (59). Leptin to increase central sympathetic function, in particular renal sympathetic activity (60). Activation of sympathetic nervous system induces hypertension(61), (45), (62). Left ventricular hypertrophy may be associated with increased sympathetic activity by increasing cardiac afterload (49). Diabetic patients have cardiac autonomic dysfunction, which was positively correlated with increased leptin levels, regardless of the amount of visceral fat (63). In turn, leptin, promotes insulin resistance and type 2 diabetes. (55). Diabetes is known to cause vascular changes, hypertension, heart valve changes, coronary artery disease, leading to HFpEF (64).

LEPTIN AND INFLAMMATION

Lately, the term “meta-inflammation” has been used to describe the correlation between metabolic stress induced by conditions such as diabetes, obesity, insulin resistance and non-alcoholic fatty liver disease and chronic inflammation (65). Activation of proinflammatory pathways is a remarkable feature in HFpEF patients (66), (67) which also coincides with aging-induced inflammation - “inflammaging”. Meta-inflammation state can lead to cardiac remodeling which eventually predispose to HFpEF. The greatest evidence of systemic inflammatory state in HFpEF patients comes from data of peripheral blood biomarkers, which commonly identify elevated levels of inflammatory biomarkers including CRP, IL-1β, IL-6, IL-10, immunoglobulin-like transcript 6, TNFα, and myeloperoxidase (68), (69), (70), (71). This inflammatory state damages endothelial cells, which leads to secretion of MPO by neutrophils. MPO then reduces NO availability (72), (50). Both of these exaggerate the inflammatory response. Upon the demise of neutrophils, they shed interleukin-6 receptors that triggers surrounding endothelial cells to engage in the recruitment of additional monocytes and

macrophages (73). Subsequently intensifying the inflammatory reaction. The most explored inflammatory pathway involves the nucleotide oligomerization domain-like receptor family, pyrin domain-containing (NLRP3) inflammasome with the subsequent cleavage and activation of IL-1β, IL-6, IL-12, IL-18. Several studies have demonstrated the central role of NLRP3 inflammasome in cardiovascular diseases (74), (75), (76), (77), (78). When tissue is damaged, molecules such as ATP, angiotensin II, fatty acids and glucose are released. The presence of these molecules activates NLRP3 in a 2-step way (79). Firstly, way there is a priming signal that leads to the transcription of IL-1β and NLRP3 precursors. Secondly, the activating signal such as ATP and urate crystal reduces in intracellular potassium and increase ROS while assembling the inflammasome. Activation of NLRP3 in the cardiomyocytes enhances local cardiac inflammation and leads to cell death (80). Inhibition of NLRP3 has been shown to prevent inflammasome activation and cardiac cell death, hence reducing damage (80) and therefore may represent a potential treatment target in HFpEF. Among others, Leptin, has a pro-inflammatory effect. It increase exspresion of IL-1β, IL-6, IL-12, TNF-α and macrophage inflammatory protein (MIP)-1 and reduces the expression of Il-10. (55), (42). TNF-α, IL-6 induce systemic pro-inflammatory state, cause diastolic dysfunction of the heart. This is one of the development stages of HFpEF (81) TNF-α induces the NF-κB pathway, activation of which leads to myocardial hypertrophy and apoptosis. TNF-α also causes myocardial diastolic and systolic dysfunction by releasing calcium from the sarcoplasmic reticulum (82), (33), (83).

LEPTIN AND DIASTOLIC DYSFUNCTION / FIBROSIS

Fibrosis is a pathological process that involves excessive deposition of extracellular matrix, mainly collagen, in the heart. Fibrosis causes the myocardium to become less flexible, which makes it more difficult for the left ventricle to fill during diastole. Fibrosis is one of the main mechanisms causing diastolic dysfunction in HFpEF (84).

Ricardo Fontes-Carvalho studied the relationship between leptin levels and the diastolic function of the heart. The results of this study indicate that higher leptin levels may be associated with a higher risk of diastolic dysfunction (85). In contrast, high leptin levels are not related to the contractile function of the heart (44), (85). There are numerous reports on the profibrotic effect of leptin. Continuous infusion of leptin in Balb/c mice increased expression of collagen 1α1 and periostin, and in ob/ob mice increased expression of collagen 1α1, collagen 3α1, and periostin genes, although no increase in fibrosis markers was found in these mice. An increase in collagen has been associated with myocardial fibrosis. Administration of spironolactone to Balb/c mice inhibited the fibrosis process by reducing fibrosis markers. The

response to spironolactone may explain the leptin-mediated mechanisms mediated by the mineralocorticoid receptor (46). Research shows that with the progress of aging, the level of leptin in the body increases, which causes fibrosis within the heart muscle by increasing the extracellular matrix in cardiac fibroblasts (86). According to some researchers, leptin may also mediate the intracellular accumulation of lipids and triglycerides. The activity of metalloproteinases, activated by leptin, the release of oxygen free radicals by the cardiac muscle tissue, also mediated by leptin, cause cardiac fibrosis. All this can lead to structural changes in the muscle tissue of the heart, to diastolic and systolic dysfunction of the heart, cardiomyopathy and heart failure (49), (87). On the other hand, giving db/db leptin to mice protected them from intracellular accumulation of triglycerides. Suprisingly, HFpEF with atrial fibrillation has lower leptin levels than HFpEF without atrial fibrillation (88). On the other hand, another study showed that elevated leptin levels were associated with the risk of recurrence of AF. Such a discrepancy could be due to differences in the age, degree of obesity or overweight of patients, or even the degree of cardiac fibrosis. (89); (88). Researchers believe that leptin cannot be a marker in the assessment changes in the myocardium in the course of coronary artery disease due to the lack of coherent information on the action of leptin and the occurrence of accompanying diseases that often accompany elevated leptin levels. These diseases themselves also carry the risk of cardiac diseases (90).

LEPTIN AND OBESITY AND BODY FAT

Leptin, which is elevated in obese individuals, negatively affects HFpEF by enhancing inflammatory processes and metabolic disorders. High leptin levels promote the accumulation of visceral fat and stimulate oxidative stress, which exacerbates cardiovascular dysfunction (68). Administration of recombinant leptin to obese individuals is not conducive to weight loss and appetite reduction, although in patients with congenital leptin deficiency, such administration of leptin has had its positive effects skutki (55). The lack of response in obese individuals may be due to leptin resistance resulting from hyperleptinemia. In the study of the relationship between the development and severity of coronary artery disease and the level of adiponectins, including leptin, echographic parameters and the level of adiponectin were compared. This study failed to confirm this relationship, despite conflicting opinions other experts (68).

EPICARDIAL FAT AND INFLAMMATION

In obese female patients with HFpEF, changes in the amount and biology of epicardial adipose tissue can be found. This is also accompanied by local inflammation within the heart muscle adjacent to the adipose tissue. Leptin, secreted by the epicardial adipose tissue, has not only a local, but also a systemic effect. In obese people, visceral and epicardial adipose tissue causes an inflammatory process that can affect various organs, including the kidneys, lungs, liver, causing fibrosis of these organs (44).

PROTECTIVE EFFECTS

On the other hand, there are reports that leptin may protect against left ventricular hypertrophy. It reduces appetite and increases energy expenditure, which can lead to weight loss and improvement in hypertension, sleep apnea, and metabolic disorders such as hyperinsulinemia and lipotoxicity. Leptin may act as a protective factor against HFpEF by reducing body weight. Therefore, additional studies may be needed to confirm the dependence of HFpEF development on high leptin levels (61), (91). In obese women, elevated leptin levels were positively correlated with lower left ventricular mass and stiffness, and the results of studies on left ventricular hypertrophy in hyperleptinemia may be biased by obesity itself, which is itself a risk factor for cardiovascular disease (92); (92). To counterbalance the above arguments, treatment with leptin ob/ob mice that had previously been given bacterial lipopolysaccharide for some time resulted in reduced oxygen free radical release, reduced inflammation, and increased antioxidant production. (93).

The level of leptin depends on the amount of body fat. There is a study, contrary to those presented earlier, that leptin can neutralize the pro-inflammatory effects of TNF-α. In catechetical patients with heart failure, not only muscle tissue is destroyed, but also adipose tissue, therefore the level of leptin in the blood decreases, and with it the protective effect of leptin decreases (94). Leptin signaling defect in mice reduced cardiac tissue resistance to stress, intracellular lipid accumulation and, as a result, led to heart failure (44). Leptin signaling mitigates post-MI cardiac injury by directly activating STAT3 and AMPK in cardiomyocytes, reducing hypertrophy, apoptosis, and inflammation, and preserving cardiac structure, function, and metabolism. Loss of leptin signaling in cardiomyocytes worsens cardiac outcomes after MI, highlighting its role in maintaining glycolytic metabolism and mitigating ischemic damage via STAT3 and AMPK activation. These findings suggest impaired leptin signaling reduces AMPK activity and increases hypertrophy, underscoring its importance in post-MI recovery (95).

CONCLUSIONS

Heart failure with preserved ejection fraction (HFpEF) is a complex clinical syndrome with a multifactorial pathogenesis. Leptin by its action can contribute to the development of HFpEF in various mechanisms. On one hand, leptin may offer protective effects against left ventricular hypertrophy. On the other hand, it can promote inflammation, oxidative stress, and myocardial fibrosis, all of which contribute to diastolic dysfunction. Additionally, leptin influences the renin-angiotensin-aldosterone system and endothelial function, potentially exacerbating HFpEF. Hyperleptinemia can lead to leptin resistance, suggesting that the diminished response to leptin may contribute to the development of HFpEF. Further research is necessary to confirm these hypotheses. A deeper understanding of leptin's role in HFpEF pathogenesis could pave the way for innovative and effective therapeutic strategies.

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