Review Article

Efficacy of Semaglutide in Modulating Cardiac Remodeling in Mice: A Review of Mechanisms and Outcomes

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Highlights

- Semaglutide significantly mitigates cardiac hypertrophy, leading to improved cardiac function.
- Semaglutide treatment reduced the expression of cardiac inflammatory markers.
- Semaglutide reduces oxidative stress and apoptosis, minimising cardiac complications.

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ABSTRACT

Objective: This review evaluates the efficacy of semaglutide in reducing cardiac hypertrophy and enhancing cardiac function in mouse studies.

Methods: A literature search was conducted using databases such as PubMed, Google Scholar, SpringerLink, Cochrane, Nature, JACC, and ScienceDirect. Keywords included "semaglutide," "cardiac remodeling," "heart failure," "heart failure with preserved ejection fraction (HFpEF)," and "cardiac hypertrophy." Studies involving male and female mice that discussed the effects of semaglutide on hypertrophy, oxidative stress, inflammatory markers, and cardiac remodeling were included. Data were extracted using the PICO framework.

Results: Semaglutide consistently led to reductions in body weight, fat mass, tissue-specific inflammation, apoptosis, and oxidative stress in mice. It significantly alleviated cardiac hypertrophy, as evidenced by decreased heart weight and left ventricular mass, and improved cardiac output through enhanced cellular architecture. Inflammatory markers such as tumor necrosis factor α, interleukin 6, and atrial natriuretic peptide were notably reduced. Fibrosis was significantly attenuated at both molecular and histological levels, with decreased collagen deposition and lower markers such as collagen 1a1 and collagen 3a1. Oxidative stress markers NADPH oxidase 2 and malondialdehyde were reduced, accompanied by increased antioxidant enzymes, including superoxide dismutase and catalase. Additionally, semaglutide reduced apoptosis, evidenced by lower levels of Bcl-2-associated X protein (BAX) and slightly decreased caspase-3.

Conclusion: The results demonstrate the significant potential of semaglutide for managing cardiac remodeling. Semaglutide showed considerable cardioprotective effects through the regulation of hypertrophy, oxidative stress, inflammation, apoptosis, fibrosis, and lipid metabolism. These benefits suggest its viability as a promising therapeutic agent for cardiac disorders. Nonetheless, more clinical trials, particularly in humans, are required to validate these findings and determine appropriate dosing.

Keywords: Cardiac Remodeling; Cardiac Hypertrophy; Cardioprotection; Heart Failure; Oxidative Stress; Inflammation; Apoptosis; Semaglutide; Glucagon-Like Peptide

Introduction

Cardiac remodeling (CR) refers to changes occurring at the molecular, interstitial, and cellular levels, resulting in alterations in the heart's mass, shape, size, geometry, and function after cardiac injury.[1]

These changes can occur in response to pathological or physiological stimuli, such as long-term hypertension or periodic increases in workload due to exercise, respectively.[1]

CR has been linked to pathologies such as myocardial infarction, aortic stenosis, hypertension, myocarditis, and valvular regurgitation.[2] In rare cases, myocardial infarction has also been reported as a delayed complication following biologic therapies such as rituximab, highlighting the importance of posttherapy surveillance and inflammatory mechanisms that may contribute to myocardial stress and injury.[3] Adaptive responses ensue to preserve cardiac function. The initial response to injury is cardiomyocyte hypertrophy and thickening of the ventricular walls. Progressively, CR can become maladaptive, with key changes in pathological CR being decreased sarcoplasmic / endoplasmic reticulum calcium adenosine triphosphatase 2a (SERCA2a) activity contributing to reduced calcium reuptake in the sarcoplasmic reticulum; overreliance on glycolysis rather than fatty acid oxidation; re-expression of fetal genes; increased oxidative stress and inflammation; cardiomyocyte death by apoptosis and autophagy; fibrosis and changes in the extracellular matrix; and impaired angiogenesis.

Signaling pathways are also involved in pathological CR. Pathways include G protein–coupled receptor signaling, calcium/calmodulin-dependent kinase pathway, and protein kinase C pathway.[4] Emerging regulators of CR include noncoding RNAs, such as microRNAs and long noncoding RNAs, which influence gene expression and signaling pathways involved in CR. 4 Moreover, increased oxidative stress and inflammatory responses post–myocardial infarction may further exacerbate pathological remodeling, as seen in clinical studies evaluating interventions such as intracoronary N-acetylcysteine during percutaneous coronary intervention to modulate platelet activation and reduce injury.[5]

CR is an adaptive change that occurs after cardiac injury to maintain cardiac function; nevertheless, it can worsen over time due to maladaptation, ultimately impairing cardiac function. Pathological electrical remodeling occurs because of diseases such as myocardial infarction and heart failure (HF), which impose structural stress and contribute to cardiac arrhythmias.[6]

Mechanical CR constitutes the structural and functional changes in response to mechanical stress.[7] Metabolic CR refers to the adaptive metabolic changes that occur at a cellular level in response to pathological stressors. In maladaptive remodeling, there is a shift toward glycolytic metabolism and a reduction in fatty acid utilization.[8]

Risk factors for pathological CR include sex (men are typically at higher risk); age; inherited factors relating to cardiac geometry; ethnicity (African American and Hispanic individuals have greater left ventricular mass than White individuals); body weight and obesity; lifestyle factors such as smoking, physical inactivity, and lower socioeconomic status; structural heart diseases, including hypertension, valvular heart disease, and myocardial infarction; metabolic factors such as hyperlipidemia and metabolic syndrome; and chronic kidney disease.[9]

Semaglutide is a glucagon-like peptide-1 (GLP-1) analog and a GLP-1 receptor agonist. It is administered to lower blood glucose levels by increasing insulin release and decreasing glucagon secretion.[10] This makes semaglutide suitable for people with diseases such as diabetes to lower cardiovascular and stroke risk; it is also used for weight loss.[10] Semaglutide has been associated with improved physical function and weight reduction in patients suffering from heart failure with preserved ejection fraction (HFpEF) and obesity.[11] It has also been linked to attenuating pathological electrophysiological remodeling in patients with diabetic cardiomyopathy.[12] Studies have shown that semaglutide ameliorates cardiac hypertrophy caused by pressure overload.[13] It also has the potential to reduce doxorubicin-induced cardiotoxicity.[14]

Although preclinical studies in mouse models have demonstrated promising cardioprotective effects of semaglutide and provided valuable insights into its mechanisms and potential

benefits,[12,13,15–18] a significant gap remains in human-based research. Another important gap is the exploration of long-term outcomes, as preclinical studies are short-term, making it difficult to assess the durability of semaglutide's effects on cardiac function over time. Further, these trials relied heavily on highly controlled experimental models that do not adequately replicate the complexity and variability of physiological conditions observed in more heterogeneous biological systems. (Image 1)

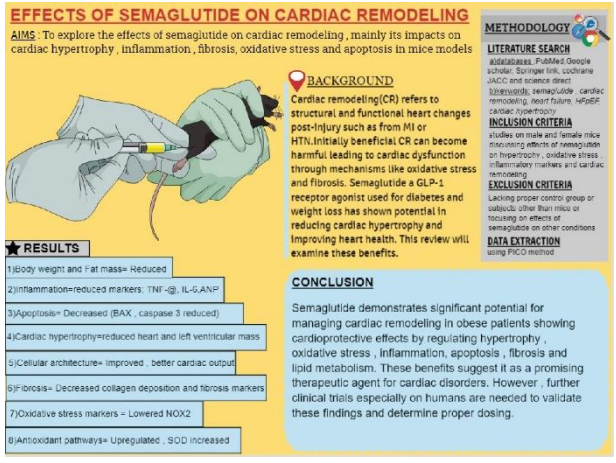

Image 1. The image presents a visual abstract of this study.

Methods

Search Strategy

This paper provides a comprehensive overview of preclinical trials demonstrating the effects of semaglutide on CR. The databases used were PubMed, Google Scholar, Cochrane, SpringerLink, Embase, Nature, JACC, and ScienceDirect. The search terms included "semaglutide," "cardiac remodeling," "heart failure," "HFpEF," and "cardiac hypertrophy." Various combinations of these terms were used with Boolean operators.

Inclusion and Exclusion Criteria

The inclusion criteria consisted of studies from inception to June 2024 involving male or female mice that focused on the effects of semaglutide on conditions such as hypertrophy, oxidative stress, apoptosis, inflammatory markers, and CR. Each trial included a control group to compare outcomes between mouse models with and without semaglutide intervention. Only papers published in English were included. Studies were excluded if they used subjects other than mice, lacked an appropriate control group, or reported effects of semaglutide primarily on obesity or other medical conditions. Studies involving an additional intervention alongside semaglutide were also excluded. These criteria ensured the review remained focused on the specific effects of semaglutide on heart health in mouse models.

Data Extraction

Data were extracted from the relevant preclinical trials using the PICO (Population, Intervention, Control, Outcome) framework. The extracted information included study characteristics, details of the experimental population (number of mice), and specifics of the intervention (dosage and duration of semaglutide administration). Controls varied but typically involved no treatment, while outcomes were recorded for key parameters such as changes in cardiac hypertrophy, myocardial injury markers, and protein expression levels. Details on study designs, statistical methods, methodology, and results were extracted to facilitate a comprehensive analysis. This approach aided in a reliable review of the included studies' findings. (Figure 1)

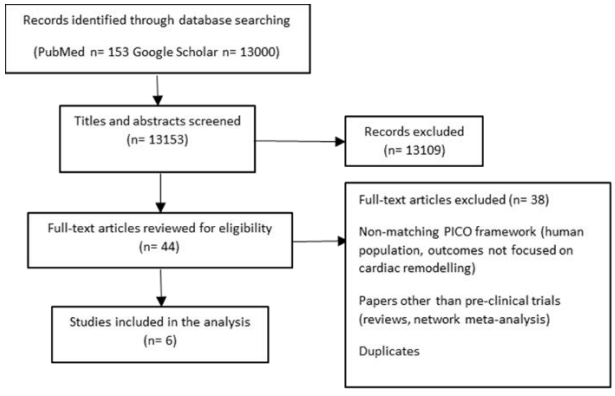

Figure 1. The image depicts the flowchart of our search strategy.

Results

Overview of The Preclinical Trials

Semaglutide has shown significant potential in addressing metabolic and cardiovascular issues in mice. Across multiple studies, semaglutide consistently reduced body weight and fat mass, improved lipid profiles, and decreased systemic and tissue-specific inflammation.[12,13,15-18]

Specifically, it reduced heart weight and left ventricular mass, indicating a mitigation of cardiac hypertrophy.[13,16-18] Histological analyses revealed less myocardial fibrosis, improved myocardial cell organization, and reduced markers of oxidative

stress, such as NADPH oxidase 2 (NOX2) and malondialdehyde (MDA).[16,18] Furthermore, semaglutide increased antioxidant enzymes like catalase (CAT) and superoxide dismutase (SOD)2, and upregulated pathways involving GPX1, SOD1, PRDX1, PRDX2, GSTP1, and GPX3. 20 The treatment also lowered inflammatory markers, including tumor necrosis factor α (TNF-α) and interleukin 6 (IL-6), and reduced apoptosis-related proteins, including BAX and caspase-3. These findings suggest that semaglutide effectively improves cardiovascular health by reducing oxidative stress, inflammation, apoptosis, and fibrosis, highlighting its therapeutic potential in managing obesity-related complications.[16,18] (Table 1)

Table 1. Characteristics of preclinical trials of semaglutide

Author, year	Study Design	Subject Population	Dietary Intervention	Dose and Duration of Semaglutide	Specific Markers Measured	Primary Outcome
Yan et al, 2024	Animal trial	6-week-old male C57BL/6J mice	Nonspecific	0.15 mg/kg/wk for 8 wk	CX43, blood glucose, Sirt1, AMPK, ECG	Improved cardiac dysfunction and oxidative stress
Ma et al, 2024	Animal trial	Male mice	Irradiated chow diet	4.0, 12.0, or 60.0 μg/kg/d for 8 wk	Blood glucose, cholesterol, EF, FS, LVIDd, ANP, BNP mRNA levels, CSA, HW/BW, LW/BW, HW/TL	Improved myocardial hypertrophy and cardiac dysfunction induced by TAC
He et al, 2024	Animal trial	Adult male Sprague-Dawley rats	None	1 mg/kg/wk for 4 wk	Ventricular dimensions, ANP, MYH7, COX II, LC3II/LC3I, NLRP3, IL-18, caspase-1	Improved left ventricular hypertrophy
Withaar et al, 2023	Animal trial	Female C57BL/6J mice	High-fat diet	Uptitrated over 5 d to 9 nmol/kg/d; maintained for 23 d	Exercise capacity, fasting glucose, glucose tolerance, body mass composition (fat, lean, fluid mass), cardiac dimensions, collagen decomposition, cardiomyocyte cross-sectional area, passive stiffness of cardiomyocytes, total ketone bodies, RNA sequencing, ANP, IL-6	Improved cardiac function, LV hypertrophy, and lung congestion
Pan et al, 2022	Animal trial	6-week-old male C57BL/6 mice	High-fat chow	30 nmol/kg/d	Ventricular dimensions, TC, TG, LDL-C, HDL-C, IL-6, TNF-α, MDA, ROS, collagen content	Improved cardiac function, inflammation, and oxidative stress levels
Li et al, 2020	Animal trial	Male Sprague-Dawley rats, 4–6 wk old	None	0.9, 0.3, or 0.1 mg/kg for 8 wk	ROS, CK, LDH, SOD, MDA	Improved apoptosis of H9C2 cells

AMPK: adenosine monophosphate–activated protein kinase; ANP: atrial natriuretic peptide; BNP: B-type natriuretic peptide; CK: creatine kinase; COX II: cytochrome-c oxidase subunit II; CSA: cross-sectional area; CX43: connexin 43; d: day; ECG: electrocardiogram; EF: ejection fraction; FS: fractional shortening; HDL-C: high-density lipoprotein cholesterol; HW/BW: heart weight/body weight; HW/TL: heart weight/tibia length; IL-6: interleukin 6; IL-18: interleukin 18; LDH: lactate dehydrogenase; LDL-C: low-density lipoprotein cholesterol; LVIDd: left ventricular internal diameter in diastole; LV: left ventricular; LW/BW: lung weight/body weight; MDA: malondialdehyde; MYH7: β-myosin heavy chain 7; NLRP3: NOD-like receptor family pyrin domain–containing 3; RNA: ribonucleic acid; ROS: reactive oxygen species; Sirt1: sirtuin 1; SOD: superoxide dismutase; TAC: transverse aortic constriction; TC: total cholesterol; TG: triglycerides; TNF-α: tumor necrosis factor α; wk: week

Semaglutide Effects on Cardiac Hypertrophy

Semaglutide significantly mitigates cardiac hypertrophy, which is common in obesity and metabolic disorders, thereby improving cardiac function.[16,17] In obese mice, semaglutide reduced heart weight and left ventricular mass, which are key indicators of hypertrophy. Histological analysis showed less myocardial fibrosis, smaller cardiomyocytes, and improved cellular architecture, correlating with better cardiac output and reduced stress markers.[16,17] The mechanisms include reduced expression of prohypertrophic and profibrotic markers (transforming growth factor β, connective tissue growth factor) and anti-inflammatory and antioxidant properties. Semaglutide lowered systemic and cardiac-specific inflammatory cytokines (TNF-α and IL-6) and oxidative stress markers (MDA and reactive oxygen

species [ROS]), reducing pathological heart remodeling.[16,17] In mice fed a high-fat diet and in a type 2 diabetes model, semaglutide significantly reduced the heart weight to body weight ratio and left ventricular mass, indicating effective mitigation of cardiac hypertrophy.[13,18] Histological analysis revealed improved myocardial cell organization, reduced myocardial fibrosis, and decreased oxidative stress markers such as NOX2 and MDA, emphasizing the role of semaglutide in ameliorating cardiac structural abnormalities associated with hypertrophy in diabetic conditions.[13,18]

Effects of Semaglutide on Inflammatory Markers

Biomarkers released during inflammation act as indicators of inflammatory diseases. Withaar et al[20] observed that mice subjected to a strict exercise and diet regimen and treated with semaglutide showed reduced levels of cardiac inflammatory markers, including atrial natriuretic peptide, IL-6, galectin 3, and growth differentiation factor 15, highlighting the anti-inflammatory effects of semaglutide.[18] Moreover, weight-bearing swimming training and semaglutide treatment in mice led to lowered levels of the inflammatory proteins nuclear factor kappa B (NF-κB), TNF-α, and IL-1β when measured by Western blot. NF-κB regulates the production of inflammatory factors such as TNF-α and IL-1β. In addition, the control group showed increased levels of the inflammatory enzymes creatine kinase and lactate dehydrogenase, whereas semaglutide-treated mice showed reduced levels of creatine kinase and lactate dehydrogenase, demonstrating the impact of semaglutide in mitigating inflammation and protecting against cardiac damage under strenuous conditions.[14] Furthermore, in mice with pressure overload–induced cardiac hypertrophy, inflammatory signaling pathways (NOD-, leucine-rich repeat [LRR]– and pyrin domain–containing protein 3 [NLRP3], caspase-1, and IL-18), measured by Western blot, were significantly reduced in the semaglutide-treated group compared with the control group.[13] Moreover, inflammatory cell infiltration assessed by hematoxylin-eosin (H&E) staining was significantly higher in the control group than in the semaglutide-treated group. This demonstrates that semaglutide reduces cardiac hypertrophy by suppressing the activation of NLRP3 inflammasomes.[13] In mice with diabetic cardiomyopathy, semaglutide treatment not only lowered blood glucose levels but also reduced inflammation, demonstrating that its cardioprotective effects extend beyond its hypoglycemic properties to include anti-inflammatory benefits.[12]

Effect of Semaglutide on Fibrosis

Fibrosis involves excessive extracellular matrix and collagen deposition, leading to CR and myocardial tissue stiffening. Mice subjected to a strict exercise and diet regimen that were treated with semaglutide showed reduced fibrosis on molecular and histological levels and decreased levels of collagen 1a1, collagen 3a1, and tissue inhibitor of metalloproteinase 1 compared with the control group, illustrating the effect of semaglutide in attenuating fibrosis.[18] As discussed previously, semaglutide reduces the expression of TNF-α, an inflammatory marker that promotes the production of other inflammatory factors leading to fibrosis and hypertrophy, thus playing a critical role in reducing fibrosis.[14] In mice with myocardial hypertrophy and cardiac dysfunction induced by transverse aortic constriction, semaglutide treatment mitigated collagen deposition and reduced collagen volume in the heart, thereby alleviating fibrosis. Lowered levels of atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP), which play a crucial role in regulating fibrosis, alongside decreased levels of collagen 1 and collagen 3 (ANP and BNP levels: $F(7,40)=138.8$; $P=5.2 \times 10^{-26}$; collagen I and collagen III: $F(7,40)=82.22$; $P=1.0 \times 10^{-21}$) demonstrate the efficacy of semaglutide in reducing myocardial fibrosis.[17]

Furthermore, the reduction of extracellular matrix proteins by semaglutide showcases its potential as an effective antifibrotic therapeutic agent.[17]

Effects of Semaglutide on Oxidative Stress and Apoptosis

Semaglutide significantly reduces oxidative stress and apoptosis, playing a vital role in managing cardiovascular complications in obesity and diabetes. In mice with diabetic cardiomyopathy,

semaglutide treatment markedly decreased NOX2 levels, a key component of oxidative burst ($P<0.05$).[12] Antioxidant enzymes CAT and SOD2 levels increased significantly ($P<0.01$ and $P<0.001$, respectively), indicating reduced oxidative stress.[12] A TUNEL assay revealed reduced cardiomyocyte apoptosis in semaglutide-treated mice.[12] Functional enrichment analysis in weight-loss mice highlighted the upregulation of antioxidant pathways involving GPX1, SOD1, PRDX1, PRDX2, GSTP1, GPX3, and G6PD. 20 Semaglutide-treated mice also showed decreased MDA levels ($P<0.05$) and increased SOD levels, suggesting reduced oxidative stress.[14] In lipopolysaccharide (LPS)-induced oxidative stress in mice, apoptosis-related proteins BAX, BCL2, and caspase-3 were increased. Semaglutide treatment significantly reduced BAX ($P<0.01$) and slightly but not significantly decreased caspase-3 ($P>0.05$), indicating reduced myocardial cell apoptosis.[14] Thus, semaglutide mitigates myocardial apoptosis.[14] The expression of cardiac proteins Apo2 and CAT is linked to the peroxisome proliferator–activated receptor (PPAR) signaling pathway and peroxisomes. Activation of the PPAR signaling pathway increases lipid metabolism. Pan et al[16] observed that oxidative stress levels are significantly higher in the adipose tissue of obese mice. In addition, peroxisome hyperactivation exacerbates these oxidative effects. In obese mice, semaglutide treatment reduced the expression of these cardiac proteins, demonstrating its cardioprotective effects.[16]

Discussion

Semaglutide is a GLP-1 receptor agonist primarily used in the management of type 2 diabetes. It functions by enhancing insulin secretion, inhibiting glucagon release, and slowing gastric emptying, thereby improving glycemic control.[19] Current evidence suggests that, beyond its hypoglycemic effects, semaglutide also exhibits weight loss and cardioprotective effects and can help reduce cardiac hypertrophy and HFpEF.[13] These effects are attributed to various mechanisms, such as improving cardiac function by enhancing mitochondrial function (mitophagy)[20]; reducing inflammation (NLRP3 inflammasome activation)[21]; reducing lipid synthesis and lipid peroxidation[16]; regulating autophagy and apoptosis[15]; and decreasing hypertrophic marker expression (ANP and MYH7).[13] These multifarious mechanisms underscore the broader cardiovascular benefits of GLP-1 receptor agonists beyond glycemic control.

An intricate disorder, obesity can be attributed to a combination of environmental variables, genetic predispositions, and individual behaviors that disrupt the balance between energy intake and expenditure.[22] This disruption leads to the accumulation of excess adipose tissue, particularly visceral fat, which is strongly linked to metabolic abnormalities and increased cardiovascular risk.[23] Studies show that semaglutide enhances appetite regulation, gastric emptying, and potentially fat metabolism, thereby enhancing satiety and reducing appetite. This reduction in caloric intake addresses a vital aspect of obesity management. Furthermore, semaglutide may elevate energy expenditure through mechanisms that could involve improved mitochondrial function or greater metabolic efficiency.[16,18-24]

A primary benefit of semaglutide treatment is its ability to diminish visceral fat more than subcutaneous fat deposits. This targeted reduction is critical because visceral fat is directly linked to cardiovascular disease and other metabolic diseases. Furthermore, semaglutide improves numerous metabolic parameters, including glycemic control, lipid profiles, and inflammatory indicators, which all contribute to lowering cardiovascular risk in individuals with obesity and metabolic syndrome.[18,25]

Oxidative stress, resulting from an imbalance between ROS production and the body's antioxidant defenses, is a key pathological mechanism linking type 2 diabetes mellitus (T2DM) to cardiovascular complications.[26] Adenosine monophosphate–activated protein kinase kinase (AMPK)– and sirtuin 1 (Sirt1)–mediated metabolic signaling pathways play important roles in alleviating oxidative stress, especially in the context of diabetic cardiomyopathy. The downregulation of Sirt1 and AMPK in diabetic hearts results in insulin resistance, mitochondrial dysfunction, and compromised antioxidant defense, thereby contributing to ROS generation.[27] A study revealed decreased expression of Sirt1 and phosphorylated AMPK (p-AMPK) in diabetic hearts. Still, treatment with semaglutide reversed this trend and restored Sirt1 and p-AMPK protein levels, suggesting that activation of the Sirt1/AMPK

pathway is crucial for the beneficial effects of semaglutide on diabetic hearts.[12]

Moreover, enzymes such as CAT and paraoxonase 1 (PON1) help reduce oxidative stress in the heart by breaking down H_2O_2 and hydrolyzing lipid peroxides, respectively. Individuals with obesity have elevated levels of CAT and PON1, indicating increased oxidative stress.[28] Be that as it may, following semaglutide treatment, a substantial decrease occurs in the expression of CAT and PON1, indicating that semaglutide efficiently decreases oxidative stress in the heart.[16]

Severe mitochondrial damage occurs in pressure-exposed hearts, leading to structural alterations such as vacuolization, swelling, and disorganized cristae. These changes ultimately reduce the activity of the oxidative respiratory chain and adenosine triphosphate (ATP) synthesis. Diminished fatty acid oxidation leads to lipid accumulation, and increased ROS promotes lipid peroxidation, which produces toxic products such as MDA, causing further mitochondrial and membrane damage and exacerbating HF.[29] Research suggests that semaglutide may protect the heart by lowering lipid peroxidation and synthesis.[16]

Heart mitophagy dysfunction, caused by pressure overload, activates the NLRP3 inflammasome, resulting in cardiac hypertrophy.[6,8] Semaglutide has been demonstrated to greatly increase cardiac mitophagy, inhibit NLRP3 inflammasome activation, and reduce ANP and MYH7 expression levels. These effects, however, are negated when a mitophagy inhibitor is used. This evidence implies that the inhibitory effect of semaglutide on the NLRP3 inflammasome is directly related to its capacity to improve mitophagy.[13]

Many physiological and pathological processes, especially those pertaining to cardiovascular health, depend heavily on inflammation. NF-κB is one of the main regulators of inflammation. An essential mechanism that enhances inflammatory reactions is the activation of NF-κB, which in turn stimulates the release of proinflammatory cytokines, including IL-1β and TNF-α. These cytokines have profound effects on cardiomyocytes. TNF-α and IL-1β at high levels can promote the proliferation of cardiomyocytes and lead to hypertrophy and fibrosis.[30] Studies show that semaglutide treatment significantly reduces the expression of the proinflammatory cytokines NF-κB, IL-1β, and TNF-α in myocardial tissue. The decrease in cytokine expression suggests that semaglutide could impede the emergence of cardiac fibrosis and other inflammation-related problems by regulating important inflammatory pathways.[15]

ROS, oxidative stress, mitochondrial dysfunction, and decreased autophagy are induced by excessive exercise. In H9C2 cells, LPS incubation induces apoptosis; nevertheless, semaglutide administration efficiently counteracts this by lowering the expression of apoptosis-related proteins.[15] Recent research has shown that AMPK activation reduces the inflammatory response of H9C2 cells during periods of hypoxia and subsequent reoxygenation and decreases cardiomyocyte apoptosis induced by ischemia-reperfusion injury.[31] This shows that semaglutide works primarily through the AMPK signaling pathway to modulate autophagy, apoptosis, and oxidative stress, decreasing LPS-induced damage in H9C2 cells.[15]

These results highlight the necessity of including GLP-1 receptor agonists in treatment plans for patients with diabetes and cardiovascular problems. Additional clinical trials and human research are needed to investigate the long-term effects and effective dosing strategies of GLP-1 receptor agonists in varied patient populations.[16]

Compared with other GLP-1 receptor agonists, semaglutide has shown efficacy in preclinical studies and is beneficial for managing T2DM and weight loss. Its long-acting formulation improves patient adherence and offers sustained therapeutic effects, reducing the risk of major cardiovascular events. This extended-release characteristic enhances convenience and compliance, supporting comprehensive diabetes management by addressing glycemic control and cardiovascular health.[13]

Conclusion

This review research focuses on semaglutide, a GLP-1 analogue, and its diverse cardioprotective effects, particularly through the regulation of oxidative stress, mitophagy, metabolic pathways, inflammation, and apoptosis.

The literature analysis found that semaglutide

increases the production of the proteins CAT and manganese superoxide in the heart and activates the Sirt1/AMPK pathway, which guards against oxidative stress and cardiac steatosis. Additionally, the decrease in oxidative stress indicators like CAT and PON1 following semaglutide administration lends credence to its protective effect in cardiac tissues.

Moreover, the analysis also signified the efficacy of semaglutide in mitigating the adverse effects of pressure overload–induced cardiac hypertrophy by enhancing cardiac mitophagy and inhibiting NLRP3 inflammasome activation. With regard to metabolic pathways, semaglutide was found to protect the heart by lowering lipid production and peroxidation, correcting mitochondrial defects, and supporting appropriate oxidative respiratory chain performance.

Furthermore, the analysis also evidenced that reduced levels of proinflammatory cytokines such as NF-κB, IL-1β, and TNF-α correlated directly with semaglutide therapy, thereby considerably reducing inflammation. Not only this, but semaglutide was also found to efficiently lower apoptosis-related protein expression while increasing autophagy-related proteins, minimizing cellular damage in cardiac tissues. Overall, our literature review analyzes strong evidence that semaglutide has great therapeutic promise in the treatment of cardiac disorders, particularly in obesity-related diseases and pressure overload, indicating a viable path for future investigations and application in clinical settings.

Limitations

Several limitations should be considered when interpreting the findings. First, the reliance on preclinical studies, particularly mouse models, combined with variation in experimental models (eg, high-fat diet or transverse aortic constriction), may contribute to variability in the results. Further, differences in semaglutide dosage and delivery methods (eg, oral vs subcutaneous) across studies, along with the lack of standardized dosing regimens, represent another limitation. Another limitation is the small sample sizes used in the studies, which may affect the reliability of the findings. Furthermore, the relatively short duration of the trials limits the ability to assess the long-term effects of semaglutide treatment.

Declarations:

Ethical Approval

This article does not involve patients; therefore, no ethical approval was required.

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Conflict of Interest

The authors declare no conflict of interest.

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