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EDITORIAL COMMENT

Semaglutide in Heart Failure With Preserved Ejection Fraction

Benefits Above and Beyond Weight Loss*

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Heart failure with preserved ejection fraction (HFpEF) is becoming the most common type of heart failure (HF) and unfortunately has very limited therapeutic options. HFpEF is a complex condition influenced by various risk factors such as aging, hypertension, obesity, and diabetes mellitus. Approximately 80% of individuals diagnosed with HFpEF are overweight or obese. Obesity results in systemic metabolic abnormalities, including dyslipidemia, insulin resistance, endothelial dysfunction, and chronic low-grade inflammation, which all play a critical role in the pathophysiology of HFpEF. Hypertension, combined with the metabolic stress mentioned earlier, enhances cardiac remodeling and fibrosis, and impairs diastolic function, contributing to the development of HFpEF. Therefore, addressing obesity and hypertension through lifestyle modifications and appropriate pharmacological interventions may have significant benefits in managing HFpEF. Although preclinical and clinical research studies in recent decades have resulted in significant progress in the management of HF with reduced ejection fraction, few clinical trials have reported effective outcomes for HFpEF patients. The recent EMPEROR-Preserved (EMPagliflozin outcome tRial in Patients With chronic heart Failure With Preserved Ejection Fraction) clinical trial demonstrated that sodium-glucose cotransporter 2 (SGLT2) inhibitor empagliflozin reduces the combined risk of cardiovascular death or hospitalization for HF in patients with HFpEF.[1] Treatment with SGLT2 inhibitors has been shown to improve cardiometabolic health, reduce plasma glucose levels and induce weight loss. The benefits of SGLT2 inhibitor in HFpEF suggest that novel approaches targeting the underlying cardiometabolic abnormalities associated with HFpEF could lead to effective therapies for this serious disease.

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) are a group of medications that have been successfully implemented in weight management and used effectively for lowering glucose levels in people with type 2 diabetes mellitus (T2DM). Treatment with GLP-1RAs is associated with significant reductions in major adverse cardiovascular events. Due to their potential cardiometabolic benefits, GLP-1RAs are widely investigated in the management of HFpEF. A recent preclinical study compared the effects of the GLP-1RA liraglutide and SGLT2 inhibitor dapagliflozin on various parameters in a mouse model of obesity-related HFpEF.[2] Interestingly, the study showed that liraglutide has more pronounced beneficial effects on body weight, cardiac function, and structural parameters in this preclinical HFpEF model compared with dapagliflozin.[2]

In this issue of *JACC: Basic to Translational Science*, Withaar et al[3] reported the remarkable cardiometabolic benefits of another GLP-1RA, namely semaglutide, in the same preclinical model of obesity-related HFpEF. The authors also investigated the important question "Are the cardiometabolic benefits of semaglutide in HFpEF simply caused by weight loss?" They compared the effects of semaglutide and pair feeding (PF)-induced weight loss on HFpEF to dissect the direct effects of semaglutide on HFpEF from the indirect effects caused by weight loss.

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Semaglutide treatment led to sustained weight loss in HFpEF mice, primarily because of a reduction in fat mass, which was similarly observed in the PF group.[3] However, the authors uncovered the distinct advantages of semaglutide over PF in other parameters of cardiometabolic health in this HFpEF model. Hearts of semaglutide-treated HFpEF mice showed improved cardiac function (reduced diastolic dysfunction, left ventricular hypertrophy and fibrosis) compared with the PF group.[3] Moreover, semaglutide exhibited a broader protection against extracardiac HFpEF pathologies by reducing lung congestion, improving glycemic control and enhancing exercise capacity, all of which are crucial aspects in managing HFpEF. Proteomic and single-nuclear transcriptomic analyses of the left ventricular showed that semaglutide treatment, but not PF-induced weight loss, enhanced cardiac cytoskeleton organization and improved endothelial function.[3] Interestingly, the authors showed that the GLP-1 receptor is mainly present in endothelial cells rather than cardiomyocytes.[3] This observation suggests that the beneficial effects of semaglutide on cardiac function and structure may primarily result from improved endothelial function and their interactions with other cells within the myocardium. At the systemic levels, the authors showed that semaglutide-treated mice, but not the PF mice, have improved plasma oxidative stress regulation and inflammatory state in visceral adipose tissue.[3] Together, these findings strongly indicate that semaglutide promotes cardiometabolic benefits in HFpEF beyond the indirect effects of weight loss and support the therapeutic potential of semaglutide in HFpEF.

Despite these significant findings, certain limitations should be considered when interpreting the results of this study. The study utilized a multifactorial mouse HFpEF model that combines multiple HFpEF risk factors and comorbidities (female sex, aging, obesity, and hypertension). This is in line with recently postulated research priorities for HFpEF by a National Heart, Lung, and Blood Institute Working Group[4] highlighting the need for animal models that also incorporate the effects of aging and its associated comorbid conditions. However, although the model used by Withaar et al[3] mimics important aspects of the disease, it represents only a subgroup of HFpEF patients. HFpEF also affects men and individuals with additional comorbidities and genetic factors. This multifactorial model combining 12-week high-fat diet and 4-week angiotensin II infusion in old mice results in HF with reduced ejection fraction but not HFpEF phenotype when applies to male mice.[2] Thus, other multifactorial models that incorporate the effects of aging to induce HFpEF in both sexes are needed to better replicate the complexity of HFpEF observed in humans. Validation of the presented findings in other HFpEF models would enhance the generalizability of the results and strengthen the foundation for further investigation in diverse patient populations.

Another limitation is related to the timing of semaglutide treatment initiation. In this study, semaglutide was initiated after 8 weeks of high-fat diet and at the same time as angiotensin II administration began. However, at that specific time point, it was unclear whether HFpEF phenotypes had already developed. As a result, the existing evidence cannot definitively distinguish whether the protective effects of semaglutide were mediated by preventing HFpEF development or by alleviating established HFpEF pathophysiology. Therefore, further studies are needed to evaluate the effectiveness of semaglutide as a therapeutic intervention to treat established HFpEF phenotypes and explore the potential of semaglutide as a therapeutic option for individuals with obesity-related HFpEF.

Also, it is crucial to consider the rising evidence regarding the prognostic implications of obesity, specifically body mass index, in patients with HFpEF. Observational studies have pointed to the existence of the "obesity survival paradox" in HFpEF, suggesting that once HFpEF is established, obesity confers a more favorable prognosis. However, the full explanation for this paradox remains elusive. A recent study examined the interaction of obesity and HFpEF prognosis in patients with and without T2DM.[5] The study demonstrated the obesity survival paradox in HFpEF patients without T2DM, where higher body mass index was associated with improved survival compared to the reference group. However, this paradoxical effect was not observed in HFpEF patients with concomitant T2DM.[5] These findings suggest that caution is needed when prescribing weight loss-inducing interventions (such as GLP-1RAs) to HFpEF patients and highlight the importance of considering the presence of T2DM in the management of HFpEF. Future research should further investigate the underlying mechanisms behind these complex interactions to develop more personalized therapies of HFpEF.

In conclusion, the promising findings from the study by Withaar et al[3] provide a strong rationale for further investigation of semaglutide as a potential therapeutic option for obesity-related HFpEF in clinical settings.[3] Beyond its weight-reducing effects, semaglutide exhibits multifaceted cardiometabolic benefits in HFpEF, including improved glycemic

control, enhanced exercise capacity, and structural and functional improvements of the heart.[3] Ongoing clinical trials (STEP-HFpEF trial [NCT04788511], STEP-HFpEF-DM [Research Study to Look at How Well Semaglutide Works in People Living With Heart Failure, Obesity and Type 2 Diabetes; NCT04916470], and SUMMIT [A Study of Tirzepatide (LY3298176) in Participants With Heart Failure With Preserved Ejection Fraction and Obesity; NCT04847557]) are already evaluating the effects of GLP-1RAs in HFpEF patients with and without T2DM. If the positive findings from this preclinical study are confirmed in clinical trials, semaglutide could significantly improve the management of HFpEF by targeting not only body weight but also the underlying cardiometabolic abnormalities.

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