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Glycometabolic cardiac dysfunction in HFpEF: Lessons from multi-omics studies

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ABSTRACT

Heart Failure with preserved Ejection Fraction (HFpEF) is a complex condition that stems from intricate biochemical changes in the heart tissue. The loss of metabolic flexibility, a hallmark of unhealthy myocardium, may play a role in its progression. However, the impact of myocardial metabolic changes on the development of HFpEF and the relationship with its diverse clinical presentations remains unclear. The heterogeneous nature of HFpEF poses a challenge to research and management, highlighting the pressing need for a deeper understanding of its pathophysiology and more accurate differentiation of its phenotypes. Multi-omics, driven by artificial intelligence and machine learning, is a source of inspiration in the field of HFpEF research. This method has the potential to reveal insights into the metabolic changes and phenotypes of HFpEF that were previously inaccessible. By revealing non-traditional biomarkers that go beyond basic clinical and demographic criteria, it also inspires the development of targeted therapies for specific patient groups. This review aims to explore the current understanding of how myocardial metabolic changes and metabolic inflexibility contribute to the pathogenesis of HFpEF. By drawing on the latest multi-omics studies, it also aims to identify an omics signature for HFpEF that could be instrumental in unearthing new biomarkers for diagnosis, phenotyping, risk stratification, and the development of tailored therapies, thereby advancing personalized medicine in the field of HFpEF.

1. Introduction

Heart failure with preserved ejection fraction (HFpEF) is a heterogeneous clinical syndrome characterized by diastolic dysfunction (DD), normal left ventricular ejection fraction (EF), and a variety of myocardial structural, functional, and metabolic abnormalities. HFpEF develops through complex biochemical changes in myocardial tissue, and the loss of metabolic flexibility, a hallmark of unhealthy myocardium, may contribute to its progression [1,2]. The impact of myocardial metabolic changes on HFpEF development is unclear, and it remains uncertain if the metabolic inflexibility model fits the heterogeneous nature of HFpEF [3]. In fact, HFpEF can be viewed as a systemic

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syndrome, rather than just an isolated heart condition, linked to the aging process and multiple comorbidities, including hypertension, obesity, type 2 diabetes, atherosclerosis, chronic renal disease, pulmonary hypertension, atrial fibrillation, ischemic heart disease, valvulopathy, anemia, sarcopenia, and chronic obstructive pulmonary disease [4]. Comorbidities and aging contribute to the development of HFpEF, leading to coronary microvascular dysfunction, interstitial fibrosis, and systemic inflammation primarily caused by metabolic stress and referred to as "meta-inflammation" [5]. Thus, they lead to heterogeneous phenotypic presentations of HFpEF, each requiring different management strategies and having different prognoses. Currently, three HFpEF phenotypes are defined based on demographic and clinical features: phenotype 1 consists of younger patients with few comorbidities; phenotype 2 includes older patients more likely to have atrial fibrillation and cardiorenal disease; and phenotype 3 features intermediate-aged individuals with a high burden of comorbidities like type 2 diabetes and obesity [4,6]. The heterogeneity of HFpEF complicates research and management, underscoring the need to understand better its pathophysiological mechanisms and to differentiate its phenotypes more precisely.

By combining omics technologies with artificial intelligence (AI) and machine learning (ML), we can develop advanced diagnostic and therapeutic models that provide profound insights into the biological processes underlying disease. The multi-omics approach, particularly promising for understanding the metabolic changes of HFpEF, its phenotyping based on non-traditional biomarkers that extend beyond simple clinical and demographic criteria, and the development of targeted therapies for specific patient groups, is a source of inspiration for further research and understanding in the field [7–9].

This review aims to explore the current understanding of how myocardial metabolic changes and metabolic inflexibility contribute to the pathogenesis of HFpEF. By considering the latest multi-omics studies, it also aims to identify an omics signature for HFpEF that could be crucial in discovering new biomarkers for diagnosis, phenotyping, risk stratification, and tailored therapies.

2. Methods

In conducting this comprehensive review, we utilized a range of electronic databases, including PubMed, Scopus, and Google Scholar, as well as thorough searches of reference lists. Our search strategy was strategically drafted to include critical key terms relevant to our topic, encompassing a comprehensive body of literature published between 1985 and 2025. To guarantee the highest quality of included studies, we utilized standardized assessment tools appropriate to the study design. This rigorous evaluation focused on methodological integrity, potential risks of bias, and the essential relevance to our research objectives. By adhering to these stringent criteria, we aim to deliver insights that not only inform but also inspire further exploration and understanding in the field.

3. Metabolic flexibility in physiological states and stress conditions: brief insights into pathophysiology

To evaluate how myocardial metabolic changes and metabolic inflexibility contribute to the pathogenesis of HFpEF, it is essential to explore the concept of metabolic flexibility and its implications in physiological states and stress conditions.

Metabolic flexibility refers to the heart's ability to adapt its metabolism to meet varying ATP demands using different energy sources. Myocardial metabolism involves intricate pathways that utilize various substrates, which are crucial for the heart's high oxygen demand. Cardiomyocytes can efficiently use various substrates based on their availability and oxygen levels, thereby maintaining energy production in both normal and pathological conditions [10–12]. Disruptions in oxygen supply or ATP production can significantly impact cardiac health, underscoring their importance in the development of heart disease. Under normal conditions, 95 % of total ATP is produced through mitochondrial oxidative phosphorylation, which requires significant oxygen consumption, especially during the activity of the electron transport chain (ETC). The remaining 5 % of ATP is generated by glycolysis, an anaerobic process [13].

Fatty acids (FAs) are the primary ATP source for the myocardium but must be continuously imported from the bloodstream due to limited intracellular storage. They bind to plasma albumin or triglycerides in lipoproteins like chylomicrons and very low-density lipoproteins (VLDL) before entering cardiomyocytes, where they undergo β-oxidation to provide intermediate products to the tricarboxylic acid (TCA) cycle and the oxidative phosphorylation [14,15]. Although FAs produce the most ATP per molecule, they require more oxygen than other substrates. During low oxygen conditions, such as ischemia, glucose becomes the preferred fuel because it is more oxygen-efficient, enabling ATP synthesis through anaerobic glycolysis and mitochondrial oxidation of pyruvate [16].

During intense physical activity or stress conditions, lactate is present in high plasma concentrations and becomes an important energy substrate. Through conversion to pyruvate by lactate dehydrogenase, lactate can enter the mitochondria and fuel oxidative metabolism [17]. During prolonged fasting or in pathological conditions such as heart failure (HF), ketone bodies, particularly β-hydroxybutyrate (βOHB), serve as an efficient alternative energy source for the heart, particularly in meeting oxygen demand. βOHB supports the TCA cycle by being converted into acetyl-CoA within the mitochondria [18]. Additionally, branched-chain amino acids (BCAAs) contribute to the TCA cycle after undergoing transamination and oxidative decarboxylation in the cytoplasm and mitochondria of cardiomyocytes [19] [Fig. 1].

Metabolic flexibility enables the heart to adapt effectively to varying energy demands and oxygen availability, ensuring optimal cardiac output in both physiological and stressful situations. It becomes clear that a loss of metabolic flexibility can contribute to several cardiovascular issues, including all types of HF and ischemic heart disease [20].

4. The role of metabolic inflexibility and mitochondrial dysfunction in the development of HFpEF

HFpEF is characterized by several key alterations that compromise myocardial function. Myocardial fibrosis is prominent and results from the accumulation of extracellular matrix proteins secreted by activated fibroblasts, which increases tissue stiffness and impairs diastolic filling [21,22]. Additionally, cardiomyocyte hypertrophy develops as an adaptive response to pressure overload, contributing to reduced ventricular compliance. These structural changes are not merely reactive bystanders; they directly contribute to DD, which is one of the hallmarks of HFpEF [23]. Another structural change is microvascular rarefaction, which occurs secondary to the reduction in small blood vessels within the myocardium. Patients with HFpEF have a lower capillary-to-myocyte ratio than nonfailing hearts, which means reduced blood flow reserve at the tissue level. This loss of capillary density limits oxygen and nutrient delivery to cardiac tissue, promoting local ischemia and amplifying metabolic stress, which worsens cardiac performance and fuels disease progression [24]. Additionally, elevated ventricular filling pressures in HFpEF can compress the microvasculature, creating a vicious cycle of ischemia and stiffness. Clinically, coronary microvascular dysfunction in HFpEF has been evidenced by reduced myocardial perfusion reserve on imaging and frequent angina-like symptoms despite no evidence of epicardial coronary artery stenosis [25]. All these structural alterations contribute to the development of DD, which occurs when the left ventricle (LV) has impaired relaxation and increased stiffness while maintaining a normal EF [26].

From a cellular point of view, DD is closely related to abnormalities in calcium handling within cardiomyocytes. During diastole, calcium must be rapidly sequestered in the sarcoplasmic reticulum by the

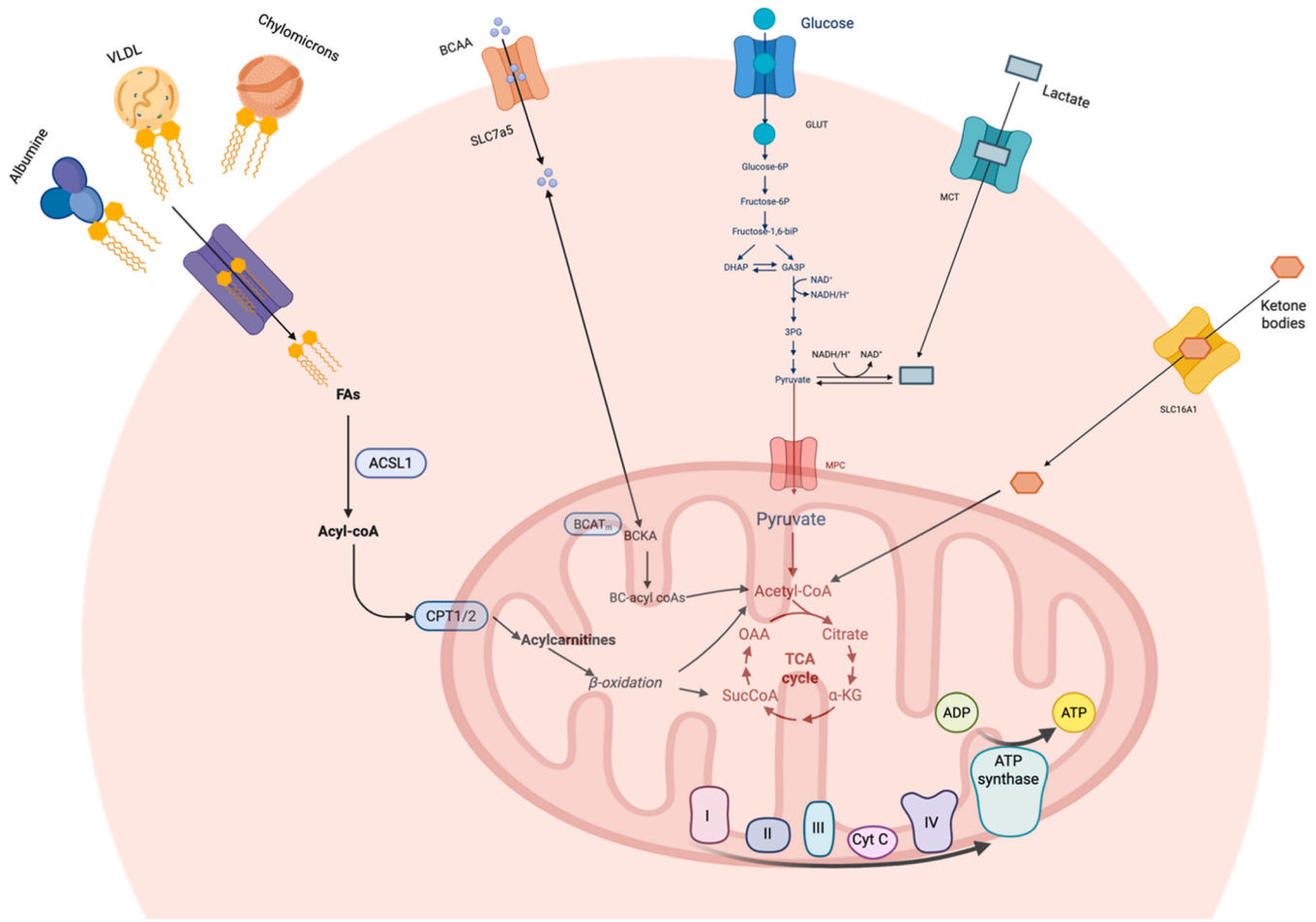

Fig. 1. The metabolic flexibility of the heart. The myocardium adapts to energy demands in various conditions, primarily using mitochondrial oxidative phosphorylation (95 %) and anaerobic glycolysis (5 %). Fatty acid oxidation contributes 40–60 % of mitochondrial ATP production, while the rest comes from pyruvate (derived by glucose and lactate), ketone bodies, and branched-chain amino acids. Although fatty acids yield more ATP per molecule, they require more oxygen, limiting their use. In contrast, glucose is the most oxygen-efficient fuel for the heart, supporting ATP synthesis during low-oxygen conditions, such as ischemia. Lactate serves as a key energy substrate during intense physical activity or stress due to its increased concentration in the blood. Ketone bodies serve as an alternative energy source during fasting or in conditions such as heart failure, providing a more oxygen-efficient energy option than fatty acids. BCAA support contractile function in various physiological and pathological conditions. Acetyl-CoA: Acetil-Coenzima A, ACSL 1: Acyl-CoA Synthetase Long-chain family member 1, Acyl-coA: Acil-Coenzima A, ADP: Adenosina Difosfato, α-KG: Alfa-Chetoglutarato, ATP: Adenosina Trifosfato, BC-acyl coAs: Branched-Chain acyl-CoAs, BCAA: Branched-Chain Amino Acids, BCATm: mitochondrial Branched-Chain Amino Acid Transaminase, BCKA: Branched-Chain Keto Acids, CPT1/2: Carnitina Palmitoiltransferasi 1 e 2, Cyt C: Citocromo C, DHAP: Dihydroxyacetone Phosphate, Fas: Fatty acids, MCT: Monocarboxylate Transporter, MPC: Mitochondrial Pyruvate Carrier, NAD^+: Nicotinammide Adenina Dinucleotide (oxidized), NADH: Nicotinammide Adenina Dinucleotide (reduced), OAA: Ossaloacetato, SLC16A1: MCT isoform specific for the transport of ketone bodies, SLC7a5: Solute Carrier Family 7 Member 5, SucCoa: Succinil-Coenzima A, TCA cycle: Ciclo degli acidi tricarbossilici.

sarcoplasmic reticulum calcium-ATPase pump (SERCA2a) and extruded through the Na+ /Ca2 + exchanger to allow myofilament relaxation. In HFpEF, SERCA2a activity is often energetically limited and functionally downregulated. It leads to a prolonged transient calcium decay and incomplete relaxation of myofilaments in late diastole [27]. The result is an increase in diastolic cytosolic calcium, which keeps actin-myosin cross-bridges active, hindering myofilament relaxation and resulting in increased resting tension [28]. Being a highly ATP-dependent process, altered SERCA activity in HFpEF is related to the reduced ATP production resulting from early mitochondrial dysfunction observed within unhealthy cardiomyocytes. Structural assessments, including electron microscopy, have demonstrated disorganized mitochondrial morphology, characterized by altered cristae architecture, variable organelle size, and reduced mitochondrial density [29]. These morphological changes are accompanied by evident functional impairments, with a reduction in mitochondrial oxidative phosphorylation capacity and ATP synthesis. Additionally, mitochondrial dysfunction promotes excessive generation of reactive oxygen species (ROS), particularly from complexes I and III of the ETC. Elevated ROS levels can lead to oxidative damage of proteins, lipids, and DNA, further impairing mitochondrial function and promoting pathological remodeling [30]. Mitochondrial failure contributes to a state of "energy starvation" in the myocardium, and even modest reductions in ATP availability can delay myocardial relaxation and promote elevated filling pressures [30,31]. Multiple comorbidities associated with HFpEF may also affect the affinity of SERCA for calcium by modifying the phosphorylation of phospholamban, its regulator.

These findings support the hypothesis that mitochondrial dysfunction may represent an early pathophysiological feature of HFpEF and that it may be responsible for the development of the more rigid metabolic profile observed in HFpEF. However, the biochemical processes occurring in cardiomyocytes across the various phenotypic presentations of HFpEF remain a topic of ongoing debate with conflicting results reported in both preclinical and clinical studies. One possible explanation for these inconsistencies is that the characteristic metabolic inflexibility of the disease is associated with a reliance on different energy substrates, depending on the specific HFpEF phenotype presented. Hypertension and metabolic syndrome-related comorbidities appear to

exert opposing influences on cardiac substrate metabolism. In experimental models focused solely on hypertension, there is evidence of a metabolic shift favoring increased glucose utilization and reduced FAs oxidation, a pattern reminiscent of that observed in heart failure with reduced ejection fraction (HFrEF) [32]. However, whereas hypertensive models shift toward glucose utilization, animal models of metabolic dysfunction (es, db/db mice, Zucker diabetic fatty (ZDF) rats, and streptozocin/high-fat diet rat models) typically demonstrate elevated rates of FAs oxidation. This shift is likely driven by underlying insulin resistance, which impairs myocardial glucose uptake and forces a greater reliance on lipid-based energy substrates [33–35]. Metabolomics studies [36] reveal that human failing hearts, including those in HFpEF, rely heavily on FAs β-oxidation, while glucose uptake is notably diminished, even in fasting [Fig. 2]. The suppression of glucose utilization is thought to be partly driven by systemic insulin resistance, a hallmark of the metabolic syndrome frequently present in HFpEF populations. With insulin-dependent glucose uptake and oxidation impairment, the myocardium shifts toward a greater reliance on FAs metabolism [37]. In obesity and diabetes, the heart readily absorbs elevated levels of circulating free FAs. However, when the influx of FAs exceeds the capacity for oxidation, it leads to the accumulation of lipid intermediates like ceramides and diacylglycerols [38]. These lipotoxic

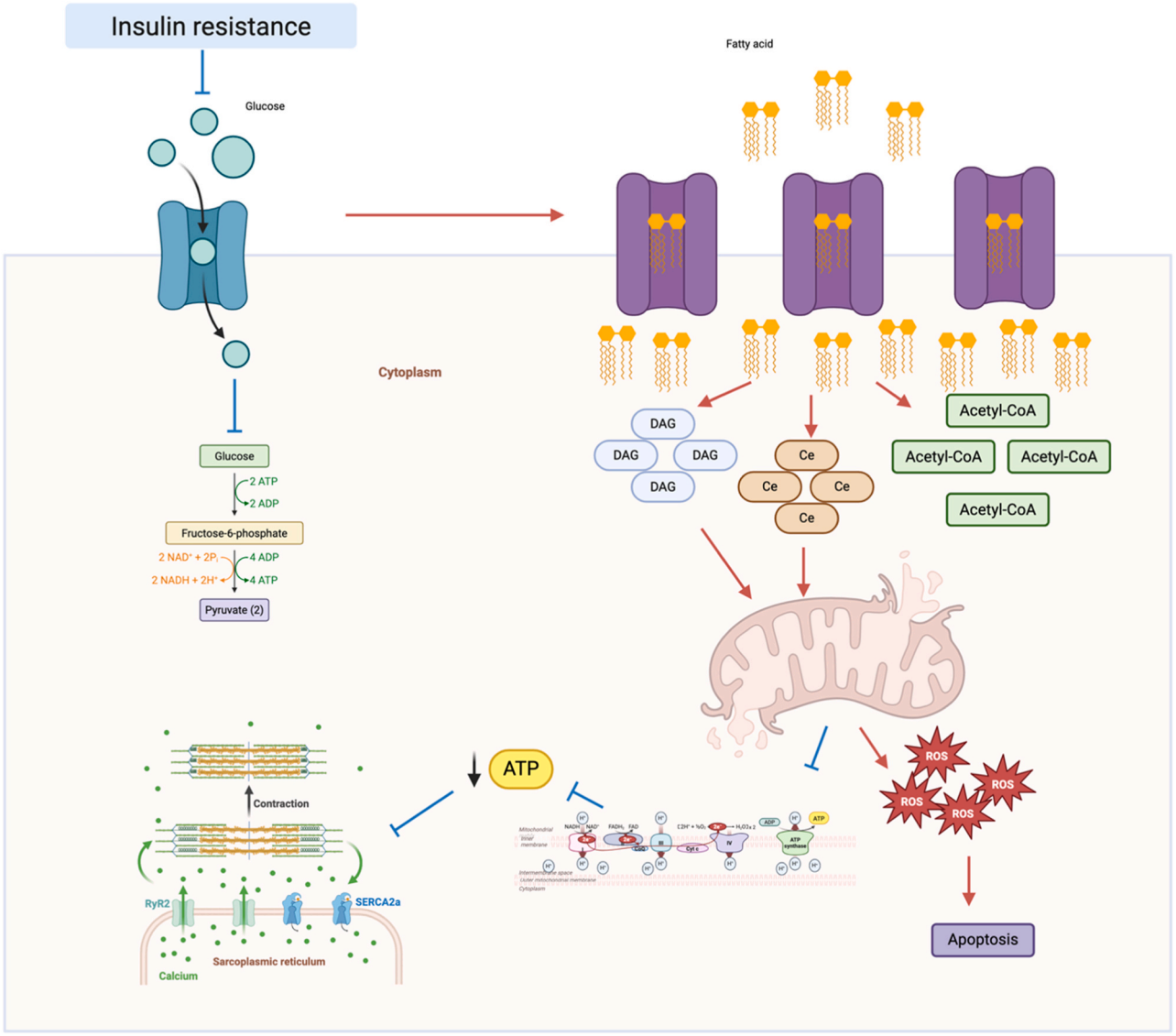

Fig. 2. Experimental metabolomics preclinical model of lipotoxic cardiomyopathy characterized by mitochondrial dysfunction in HFpEF phenotypes linked to insulin resistance: Overexpression of free fatty acid transport proteins in mouse cardiomyocytes raises energy substrate demands for β-oxidation due to the cells' glucose utilization issues linked to insulin resistance, leading to lipid intermediate accumulation, including ceramides (Ce) and diacylglycerols (DAG). These lipotoxic molecules lead to mitochondrial dysfunction, characterized by a disorganized mitochondrial morphology with an altered cristae architecture, variable organelle size, and reduced mitochondrial density. These changes result in the early downregulation of mitochondrial respiratory enzymes, which compromises oxidative phosphorylation and ATP synthesis. Modest reductions in ATP production can delay myocardial relaxation and increase filling pressures by impairing ATP-dependent diastolic processes, such as actomyosin detachment and calcium reabsorption into the sarcoplasmic reticulum. Additionally, mitochondrial dysfunction leads to the excessive production of reactive oxygen species (ROS), resulting in oxidative damage to proteins, lipids, and DNA. The damage leads to cellular injury, apoptosis, interstitial fibrosis, and stiffening of cardiomyocytes, ultimately worsening diastolic function. Acetyl-CoA: Acetil-Coenzima A, ADP: Adenosina Difosfato, ATP: Adenosina Trifosfato, Ce: ceramides, CoQ: Coenzyme Q (Ubiquinone), Cyt C: Citocromo C, DAG: diacylglycerols, e^-: Electrons, FAD: Flavin Adenine Dinucleotide, $FADH_2$: Flavin Adenine Dinucleotide (reduced), H^+: Protons (Hydrogen ions), H_2O: Water, NAD^+: Nicotinammide Adenina Dinucleotide (oxidized), NADH: Nicotinammide Adenina Dinucleotide (reduced), O_2: Oxygen, ROS: Reactive Oxygen Species, RyR2: Ryanodine Receptor 2, SERCA2a: Sarcoplasmic Reticulum Ca^{2+}-ATPase isoform 2a.

molecules contribute to increased oxidative stress, disrupt mitochondrial function, and activate pathways associated with cellular injury and apoptosis, leading to interstitial fibrosis and cardiomyocyte stiffening, which worsens diastolic function [39]. Experimental models support the theory that overexpression of FAs transport proteins in mice leads to lipotoxic cardiomyopathy characterized by DD, increased myocardial fibrosis, and hypertrophy, but need further confirmation with clinical trials [40–42]. In addition to glucose and lipid metabolism alterations, ketone bodies emerge as a possible alternative energy source in HFpEF. The heart typically oxidizes ketone bodies in proportion to their release, in direct competition with the use of FAs and glucose. The myocardium is the consumer of the highest ketone body for a unitary mass. Circulating ketone body concentrations increase in HF patients with rising cardiac filling pressures, but their significance is unclear. They may serve as more efficient energy substrates than FAs, producing more energy available for the synthesis of ATP for oxygen molecules, or potentially have cardioprotective effects by supporting the TCA Cycle and mitochondrial integrity. However, these experimental hypotheses require further clinical validation, particularly in relation to their pertinence to a specific phenotype of HFpEF [43,44]. Recent metabolomic and proteomic studies highlight increased amino acid catabolism in the HFpEF heart. Analyses of arterio-venous gradients across the human myocardium have shown a net release of nitrogen-containing amino acids, such as glutamine and alanine, suggesting an elevated rate of proteolysis and protein turnover [36]. This catabolic phenotype indicates that the heart is breaking down endogenous proteins to supply TCA intermediates via anaplerosis, further reflecting a state of metabolic inflexibility and energy stress. These changes can also contribute to the inflammation and remodeling of tissues, as the degradation of proteins can trigger immune responses and compromise cell homeostasis, suggesting that they may prevail in the phenotypes of HFpEF associated with comorbidities related to inflammation.

Considering the explanations provided, it is reasonable to conclude that mitochondrial dysfunction and metabolic inflexibility are key factors in the pathological biochemical mechanisms of HFpEF, creating an energy stress state for the myocardium. Although this metabolic reprogramming may be beneficial at first, it becomes maladaptive over time. This maladaptation favors mitochondrial dysfunction, promotes oxidative stress, and drives structural remodeling associated with HFpEF, such as fibrosis, hypertrophy, and microvascular rarefaction. It can also be hypothesized that the variation in HFpEF presentations may be linked to the utilization of different biochemical substrates, as in HFpEF phenotypes associated with metabolic syndrome and insulin resistance. Although the current findings are too preliminary to draw definitive conclusions, they have potential clinical implications and offer a glimmer of hope for future therapeutic options by identifying mitochondrial health and substrate utilization as therapeutic targets.

5. Multi-omics studies on HFpEF

Myocardial metabolic changes in HFpEF and their contribution to its development and its multiple manifestations represent a rich area for research, especially in the application of new AI and ML techniques. The identification of an omic signature for HFpEF through multi-omics studies could be crucial for shedding light on the link between these mechanisms and HFpEF, as well as for discovering new biomarkers for diagnosis, phenotyping, risk stratification, and personalized therapies.

Omics analyses are fundamental in precision medicine for tailoring medical treatment. They have been utilized to identify the metabolic fingerprints of specific individuals and groups in various pathologies and are increasingly employed to develop new risk stratification approaches in CVD [45,46]. Thus, omics studies have proven to be valuable tools to improve our understanding of the pathophysiology of HFpEF. However, this approach suffers from several significant limitations, including non-standardized methods, incomplete databases, a lack of healthy controls (HCs), and challenges in translating findings from preclinical models to clinical settings, resulting in insufficient or uncertain evidence. Additionally, omics techniques face technical limitations, such as batch effects and platform differences, which may undermine their value or lead to inconsistent results [47–49]. Some of these challenges can be addressed by integrating multiple omics analyses. This approach is promising in the study of HFpEF [50] [Table 1].

5.1. Pathophysiological insights

As in the case of HFrEF [51], a multi-omics perspective could suggest important evidence to understand the role of myocardial metabolic changes in the development of HFpEF. A metabolomic and transcriptomic study in kittens with HFpEF caused by ascending aortic banding revealed the presence of early cardiac remodeling with LV hypertrophy and interstitial fibrosis, which occurred before functional decline [52]. This cardiac remodeling correlated with alterations in 99 genes related to transcriptional regulation, epigenetic modifications, mitochondrial function, and immune response in the LV. Metabolomic analysis enlightens the link between impaired oxidative metabolism, mitochondrial dysfunction, and the early fibrotic response in HFpEF. In later stages of HFpEF, kittens at four months post-banding showed changes in gene expression in ACADVL, PDK1, and TIGAR, indicating a shift from oxidative metabolism to aerobic glycolysis. Additionally, gene alterations related to glycerolipid synthesis, protein glycosylation, serine metabolism, and post-translational modifications suggested enhanced metabolic regulation, accompanied by normalized mitochondrial dysfunction. During this stage, metabolomics revealed changes in 67 metabolites favoring glycolysis over oxidative phosphorylation and a metabolic remodeling of the amino acid superfamily responsible for cardiac fibrosis with an increase in the abundance of branched-chain amino acids (BCAAs). The findings indicate that mitochondrial dysfunction and impaired oxidative metabolism are key factors in the early stages of HFpEF development. Compensatory mechanisms, like promoting glycolysis, emerge later to enhance metabolic regulation and address mitochondrial issues. Thus, the reliance on alternative substrates and metabolic inflexibility seems to be an adaptation to mitochondrial dysfunction. However, the preclinical nature of the study highlights the need for further research to verify the roles of these biochemical mechanisms in a clinical setting.

Omics techniques have also provided support for the hypothesis that inflammation is a key pathological mechanism for HFpEF, involving mechanisms different than HFrEF, such as the PI3K−Akt and IL-6 signaling pathways. At the same time, there is a relatively minor activation of pathways involving NO and endothelial cell damage [50, 53–59]. These kinds of mechanisms, although adaptive, could play a predominant role in the pathogenesis of HFpEF phenotypes associated with comorbidities involving meta-inflammation. Further insight into the role of IL-6 and the PI3K−Akt signaling pathway certainly provides interesting insights for future research.

5.2. Novel biomarkers

Omics studies provide robust support for uncovering novel biomarkers that can enhance the diagnosis of HFpEF and augment the predictive power of traditional diagnostic factors. A clinical lipidomics study highlighted significant correlations between specific plasma lipid species and echocardiographic parameters, such as the correlation between specific phosphatidylcholines and left atrial volume (LAV) index [60]. Dutta et al. [61] examined the metabolomic and lipidomic profiles of the Framingham Offspring human cohort affected by HF, discovering that energy storage metabolites and lipids were associated with LV wall thickness and mass. Culler et al. [9] correlated 47 circulating metabolites with several echocardiographic measures and NT-proBNP among older adults without HF in the Multi-Ethnic Study of Atherosclerosis (MESA). 10 metabolites associated with glucose and amino acid metabolism correlated with at least one echocardiographic measure, with

Table 1
Summary of the current targets and results of the preclinical and clinical multi-omics studies on HFpEF.

First Autor	Sample studied	Target	Omic techniques	Main findings
Wegermann K [4]	Patients with NAFLD and HFpEF	Metabolites linked to HFpEF in NAFLD patients to identify shared mechanisms.	Serum metabolomic.	73.6 % of the fifty-three metabolites linked to HFpEF in NAFLD patients were lipid metabolites, indicating that lipid metabolism may connect HFpEF to NAFLD.
Culler KL [6]	Cohort 1: Older patients without HF (MESA cohort) Cohort 2: HFpEF Patients (Northwestern cohort)	Cohort 1: Associations between metabolites and NT-proBNP. Genetic variants linked to major metabolites correlated with echocardiographic measures and NT-proBNP. Cohort 2: Differences in metabolites between HFpEF and comorbidity-matched controls.	Serum metabolomic.	Cohort 1: Myo-inositol, glucose, dimethylsulfone, and carnitine were linked to higher NT-proBNP levels, while 2-D-mannose and acetone were associated with lower levels. Genetic analyses revealed that one of the six known loci for Myo-inositol conferred the risk of NT-proBNP. Cohort 2: Higher Myo-inositol levels were observed compared to comorbidity-matched controls.
Murashige D [33]	HF patients vs. HC	Human cardiac substrate consumption	Plasma metabolomics.	The heart with HF primarily consumed FA, using less glucose, produced more ketones and lactate, and had higher rates of proteolysis compared to HC.
Abudurexiti Mc [47]	HFpEF patients vs. HC	Compare the proteomic and metabolomic profiles of HFpEF patients and HC.	Untargeted plasma metabolomics and proteomics.	In HFpEF patients, a total of 102 metabolites and 46 proteins were significantly differentially expressed and related to enriched pathways for tuberculosis and African trypanosomiasis, revealing distinct inflammatory and immune response pathways in HFpEF compared to HC.
Jovanovic N [48]	HFpEF patients with NT-proBNP > 125 pg/ML vs. HC	Plasma lipid profiles linked to echocardiographic parameters in HFpEF.	Shotgun plasma lipidomics.	The HFpEF group showed significantly stronger correlations between cholesteryl esters and phosphatidylcholines and LAV, LV end-diastolic diameters, and HR. The HC group showed significantly stronger negative correlations between phosphatidylcholines and sphingomyelins and LV mass index and BP.
Dutta S [49]	HF patients from the Framingham Heart Study Offspring and Women's Health Initiative cohorts	Correlate plasma metabolites and lipid concentrations with echocardiographic parameters, sleep apnea, HFrEF, HFpEF, and sleep indices.	Plasma metabolomics and lipidomics.	Energy metabolites are linked to cardiac function, while energy storage metabolites and lipids are correlated with LV wall thickness and mass. Plasma cotinine levels were associated with increased time spent with oxygen saturation below 90 % during sleep.
Lai L [50]	Mouse model: 8-week-old female C57BL/6 J mice	Compare compensated, decompensated (in HF), and physiological (due to endurance training) hypertrophy.	Myocardial transcriptomics and metabolomics.	A progressive downregulation of transcripts encoding proteins and enzymes involved in FA transport and oxidation in myocytes took place during the development of HF, indicating significant regulation at the post-transcriptional level. Metabolomic signatures were observed, and it could differentiate between pathological and physiological cardiac hypertrophy, suggesting changes in carbon substrate flux within the Krebs Cycle.
Gibb AA [51]	Animal model: 2-month-old male kittens underwent aortic constriction	Define metabolic and transcriptional changes in a large HFpEF animal model.	Myocardial transcriptomics and metabolomics.	One month post-banding, mitochondrial function, and oxidative metabolism changed, returning to normal by four months. Mitochondrial dysfunction and energy deficits were observed in skeletal muscle at both early and late stages of the disease, indicating that cardiac signaling impacts peripheral tissue adaptation in HFpEF.
Liu G [52]	HF patients from the ARIC Study	Identify metabolites linked to the incidence of HF and examine their risk prediction in at-risk populations.	Untargeted serum metabolomics.	Among the sixty metabolites associated with HF, mannonate was identified. A MRS, based on selected metabolites, was associated with an 80 % increased HF risk. The highest MRS quartile had an 8.7-fold greater risk of developing HFpEF compared to the lowest quartile. Adding MRS to clinical risk factors and NT-proBNP enhanced 5-year HF risk prediction in older adults.
Wang YC [53]	HFpEF mouse model: C57BL/6 J mice on a high-fat diet and nitric oxide synthase inhibition. Validation cohorts: Cleveland Clinical patients without HF and HFpEF outpatients.	Study IPA in mouse models and two human cohorts of HFpEF.	Metagenomics and myocardial and plasma metabolomics.	In mice, dietary supplementation with IPA attenuated DD, metabolic remodeling, oxidative stress, inflammation, gut microbiota dysbiosis, and intestinal epithelial barrier damage. In the heart, IPA suppressed nicotinamide N-methyltransferase expression, restoring nicotinamide, NAD+ /NADH, and SIRT3 levels. IPA was significantly lower in HFpEF patients across two independent cohorts, indicating a protective role in both humans and mice.
Hahn VS [58]	HFpEF vs. HFrEF and HC in human cohort.	Energy source changes in HFpEF vs. HFrEF.	Myocardial and plasma metabolomics and transcriptomics.	HFpEF myocardium showed lower FA metabolites compared to HFrEF, as well as reduced ketones, TCA, and BCAA cycle metabolites, indicating insufficient use of alternative energy sources and significant energy rigidity in this syndrome.

(*continued on next page*)

Table 1 (*continued*)

First Autor	Sample studied	Target	Omic techniques	Main findings
Naeem F [59]	Penn Medicine BioBank: HFrEF patients vs. HFpEF patients vs. HC	Detect plasma metabolic signatures in HF to find biomarkers for HFpEF and HFrEF.	Plasma metabolomics.	Unsaturated medium/long-chain acylcarnitines and 3-hydroxybutyrate levels were higher in the HFrEF group compared to HFpEF and HC, while asymmetric dimethylarginine was elevated in HFpEF.
Hunter WG [60]	CATHGEN Biorepository: Patients underwent cardiac catheterization	Identify metabolic abnormalities and differentially altered pathways in HFpEF compared to HFrEF.	Plasma metabolomics.	Long-chain acylcarnitine levels were higher in HFrEF than HFpEF and, in both cases, higher than in non-HF controls, indicating dysregulated FA oxidation.
Zordoky BN [61]	Alberta HEART Project: Patients with HFpEF, HFrEF, and age-matched non-HF controls.	Uncover a novel metabolomic fingerprint of HFpEF to understand its pathophysiology and identify new biomarkers for diagnosis and differentiation from HFrEF.	Serum metabolomics.	HFpEF patients exhibited higher serum levels of acylcarnitines, carnitine, creatinine, betaine, and amino acids while showing lower levels of phosphatidylcholines, lysophosphatidylcholines, and sphingomyelins compared to non-HF controls. Medium- and long-chain acylcarnitines and ketone bodies were also elevated in HFpEF patients relative to HFrEF patients. Two novel metabolite panels identified via logistic regression can differentiate HFpEF patients from both non-HF controls and HFrEF patients.
Lanfear DE [62]	HF patients divided into derivation and validation cohorts.	Plasma metabolite profiling to predict HF	Plasma targeted metabolomics.	Identification and validation of a PMP score associated with mortality in HF subgroups, demonstrating improved survival compared to conventional predictors.
Ruiz M [63]	Cohort 1: HF patients recruited at the Montreal Heart Institute Validation cohort: HF patients recruited at Washington University	Insights into systemic metabolic perturbations in HF.	Plasma targeted and shotgun metabolomics.	Patients with HFrEF exhibit altered acylcarnitine levels, indicating FA metabolism dysregulation in mitochondria and peroxisomes, which may contribute to lipid disturbances in HF.
Bai B [65]	HFpEF patients vs. non-HF control.	Assess the link between neutrophil/lymphocyte ratio, genetic signatures, inflammation, and DD in HFpEF patients.	Transcriptomics.	An elevated neutrophil/lymphocyte ratio linked to neutrophil activation indicates systemic inflammation and worsening function in HFpEF patients, suggesting a potential role of neutrophils in the disease's pathogenesis.
Ma YL [78]	Mouse model: male C57BL/6 J mice.	Impact of Semaglutide on cardiomyocyte metabolism under pressure overload.	Myocardial-targeted metabolomics and transcriptomics.	Semaglutide improves cardiac function and reduces hypertrophy and fibrosis by modulating energy metabolism in a mouse model of pressure overload-induced HF.

BCAAs: Branched-chain amino acids, BP: blood pressure, DD: diastolic dysfunction, FA: fatty acids, HC: healthy controls, HF: heart failure, HFpEF: Heart failure with preserved ejection fraction, HFrEF: Heart failure with reduced ejection fraction, HR: Heart ratio, IPA: Indole-3-propionic acid, LAV: left atrial volume, LV: left ventricle, MRS: metabolite risk score, NT-pro BNP: N-terminal pro-B-type natriuretic peptide, PMP: prognostic metabolite profile, TCA: tricarboxylic acid cycle.

notable gender differences. Of the 10 metabolites, myoinositol was associated with higher NT-proBNP levels also in the Northwestern validation cohort that included patients with HFpEF. Additionally, genetic analysis identified one variant (rs10037610) of myo-inositol associated with increased NT-proBNP risk. To further evaluate the role of multi-omics techniques in enhancing traditional risk factors, Liu et al. [62] identified metabolites linked to HF and evaluated their predictive power over five years in individuals aged $\geq$ 65 from the Atherosclerosis Risk in Communities (ARIC) cohort compared to traditional risk factors such as clinical parameters and NT-proBNP. They identified 60 metabolites linked to HF, with 31 positively and 29 negatively associated. A metabolite risk score (MRS) was generated from 40 metabolites, indicating an 80 % increased risk of HF. Participants in the highest MRS quartile faced over five times the HF risk compared to those in the lowest. The MRS was more strongly associated with HFpEF than HFrEF, showing consistent effects across race and sex. Incorporating MRS into existing clinical risk models improved 5-year HF risk prediction by 3.3. Higher MRS levels also correlated with increased LV dimensions and pressure, but reduced circumferential strain. In addition to supporting traditional risk factors in the diagnosis of HFpEF, the identification of an omics signature has provided preliminary data to advance hypotheses on the correlation between specific metabolites and comorbidities commonly associated with HFpEF, such as exercise intolerance, central sleep apnea, and MASLD [7,52,61,63–65]. These preliminary findings are important, given the complexity of HFpEF management due to its heterogeneous nature, and hold great promise for improving and optimizing diagnostic and therapeutic pathways. However, to strengthen our understanding, further validation is essential, as the current data are preclinical or derived from population samples that fail to capture the full diversity of potential HFpEF phenotypes.

Radiomics research demonstrates significant potential to enhance cardiovascular risk prediction in HFpEF by augmenting the predictive power of traditional diagnostic methods. Epicardial adipose tissue (EAT) has garnered considerable attention due to its association with HF incidence and the occurrence of major adverse cardiovascular events (MACE). Advanced imaging and deep learning (DL) techniques for evaluating EAT radiomic features from standard non-contrast CT scans are effective in predicting HF risk in both diabetic and non-diabetic patients. This method is comparable to traditional approaches that rely on prior medical history, costly imaging tests, and invasive blood tests [66]. A novel ML model has been shown to effectively predict positive coronary artery remodeling by analyzing EAT and calcification features from low-cost or free screening non-contrast CT calcium scoring (CTCS) scans [67]. Additionally, DL models can predict MACE using features derived from EAT assessed in non-contrast CTCS images [68]. Radiomics marks a significant advancement in the creation of personalized, cost-effective strategies for preventing and managing HFpEF. It can serve as a valuable tool for assessing cardiovascular risk and evaluating the cardioprotective effects of drug therapies. This approach can enhance patient outcomes and improve quality of life.

5.3. *Differentiating between HFpEF and HFrEF*

Distinguishing between HFpEF and HFrEF is crucial for targeted therapies. The pathophysiology of HFpEF is intrinsically related to its comorbidities, while HFrEF results from myocardial damage due to

ischemia-reperfusion, infection, or toxicity [69]. The pathophysiological differences between HFpEF and HFrEF have provided an interesting starting point for the application of multi-omics in the differential diagnosis of HFrEF and HFpEF.

Efforts to identify an omic signature in the metabolic changes occurring in HFpF and HFrEF have often met with conflicting results both in animal and human trials. However, a key finding is the evidence supporting the presence of FAs metabolism dysregulation in mitochondria and peroxisomes, which plays a significant role in contributing to metabolic inflexibility characteristic of HFpEF [70–75]. The contradictory results can be attributed to the inherent limitations of omics techniques, as well as the diversity within the population samples. Adopting a more standardized approach to these methods and making a concerted effort to translate preclinical models into clinical settings with more homogeneous phenotypic characteristics will undoubtedly lead to clearer and more consistent results.

In addition to providing a ground for pathophysiological hypotheses, the application of integrated omics techniques has been used to identify potential biomarkers that distinguish between HFpEF and HFrEF. Pouleur et al. [8] revealed elevated plasma myoinositol levels in Belgian and Canadian HFpEF and HFrEF human cohorts compared to HCs. The increase was more pronounced in the HFpEF population. Higher levels of myoinositol were associated with NT-proBNP, troponin, cardiac fibrosis, impaired renal function, and poor clinical outcomes in HFpEF patients. This result suggests that myoinositol, with its potential as a valuable diagnostic and prognostic tool for HFpEF, is an area of research that holds promise for intriguing future applications.

5.4. Therapeutic targets

The application of omics techniques represents an effective strategy for identifying novel therapeutic targets. Novel preclinical results have identified two key aspects that could serve as innovative therapeutic targets: Indole-3-propionic acid (IPA) deficiency and the decrease in Xbp1s expression leading to overactivated FoxO1. IPA, derived from dietary tryptophan by gut microbes, is vital for mucosal homeostasis, mitochondrial function, reducing type 2 diabetes risk, and regulating DD in HFpEF. IPA modulates HFpEF-related dysfunction via the NAD+ / NADH pathway, elevating sirtuin 3 expression through the aryl hydrocarbon receptor (AhR), while also reducing inflammation and levels of nicotinamide N-methyltransferase (NNMT). Wang et al. [76] analyzed IPA levels in a mouse model of HFpEF. They validated their findings in human cohorts, discovering reduced IPA levels in the heart and plasma of HFpEF patients compared to HCs. Additionally, IPA supplementation in HFpEF mice improved metabolic homeostasis and reduced DD, metabolic remodeling, oxidative stress, and inflammation. Schiattarella et al. identified the Xbp1s-FoxO1 axis as a potential therapeutic target. The established link between cardiac lipid overload and HFpEF appears to result from the disruption of endoplasmic reticulum (ER) homeostasis in cardiomyocytes under disease-induced stress [77,78]. The unfolded protein response (UPR) is activated in response to ER stress, involving three transmembrane ER sensor proteins, including Inositol-Requiring Kinase 1α(IRE1α). IRE1α is crucial in generating spliced X-box binding protein 1 (Xbp1s), a potent transcription factor essential for the stress response with a cardioprotective role in HFpEF. Indeed, suppression of the IRE1α/Xbp1s pathway of the UPR is a distinct alteration seen in HFpEF and contributes to lipotoxic alterations in cardiomyocytes and cardiometabolic disease [79]. In a mouse model of HFpEF, a decrease in Xbp1s expression was associated with reduced degradation of FoxO1, which leads to lipid accumulation in the cardiomyocytes affected by HFpEF. Overactivated FoxO1 results in cardiomyocyte steatosis. Conversely, deleting FoxO1 or overexpressing Xbp1 in cardiomyocytes can improve the HFpEF phenotype by reducing cardiac steatosis. Exploring strategies to increase IPA levels, such as direct supplementation or modifying the gut microbiota, and promoting Xbp1s expression or inhibiting FoxO1, represents a promising direction for further research and potential clinical applications.

Another effective strategy for identifying novel therapeutic targets involves a multi-omics approach to study the gut microbiota. Recognizing alterations in gut microbiota composition and metabolites related to dysbiosis is essential for understanding the gut-heart axis, which plays a significant role in the multisystemic pathogenesis of HFpEF [80]. In HFpEH, the gut microbiota exhibits reduced α and β diversity, along with a lowered Firmicutes-to-Bacteroidetes ratio [81]. Additionally, pro-inflammatory flora seems to dominate over anti-inflammatory flora [82]. In addition to IPA, the production of other microbial metabolites changes during dysbiosis. In the obesity-related HFpEF rat model, serum trimethylamine N-oxide (TMAO) was significantly elevated and showed a positive correlation with the severity of diastolic dysfunction [83]. Elevated TMAO levels are an independent predictor that can be useful for risk stratification in HFpEF patients, both on their own and in conjunction with BNP levels [84,85]. Short-chain fatty acids (SCFAs) have anti-inflammatory and antioxidant properties that help prevent cardiac steatosis and heart remodeling. In cases of HFpEF, a reduction in SCFA levels in the bloodstream is associated with a decline in gut bacteria that produce SCFAs, such as Ruminococcus [81]. The gut-heart axis plays a crucial role in the development of HFpEF, making it a promising target for therapeutic interventions.

6. Therapeutic implications in HFpEF

Although emerging evidence highlights myocardial energy metabolism as a promising therapeutic target in HFpEF, effective treatment options are still lacking.

Several therapies aim to restore metabolic flexibility in the myocardium by shifting substrate utilization, improving mitochondrial function, and reducing oxidative stress [Fig. 3]. These metabolic therapies show significant potential in the treatment of HFpEF, offering hope for more effective and targeted treatments in the future.

Targeting FAs oxidation may be a promising therapeutic option. As previously described, excessive FAs oxidation in HFpEF contributes to inefficiency, as it requires more oxygen per ATP molecule than glucose. Trimetazidine and ranolazine are partial FAs oxidation inhibitors that promote a shift toward glucose oxidation. Trimetazidine inhibits mitochondrial long-chain 3-ketoacyl CoA thiolase, while ranolazine acts via late sodium current inhibition, indirectly improving metabolic efficiency. Both have shown improvements in diastolic function in experimental models, though large clinical trials in HFpEF remain lacking [86]. Recently, Serag and colleagues have demonstrated that a three-month treatment with trimetazidine improved diastolic function parameters, LV global longitudinal strain, dyspnea severity, and LDL-C levels in a small cohort of diabetic patients with DD [87]. Supplementation with L-Carnitine, an important metabolite in FAs oxidation, has improved diastolic and systolic function in hemodialysis patients [88]. However, the evidence regarding the treatment of HFpEF remains limited.

Mitochondrial dysfunction is a promising future therapeutic strategy. Nicotinamide riboside or nicotinamide mononucleotide (NMN) enhances NAD+ pools, restoring mitochondrial respiration and reducing myocardial fibrosis. Studies in Sirtuin 7 knockout mice demonstrate that treatment with NMN inhibits adverse cardiac remodeling and delays the progression of HF [89].

GLP-1 receptor agonists (GLP-1RAs), including liraglutide and semaglutide, have shown promise in targeting the metabolic abnormalities that contribute to HFpEF, especially in patients with obesity or insulin resistance. Preclinical studies suggest these agents enhance myocardial energy efficiency by improving glucose utilization and promoting FAs oxidation, reducing lipid accumulation, and preserving mitochondrial function [90]. Inflammatory signaling, particularly from visceral adipose tissue, appears attenuated with GLP-1RA treatment, even when weight loss is matched, indicating mechanisms beyond simple weight reduction [91–93]. Endothelial function is another potential target:

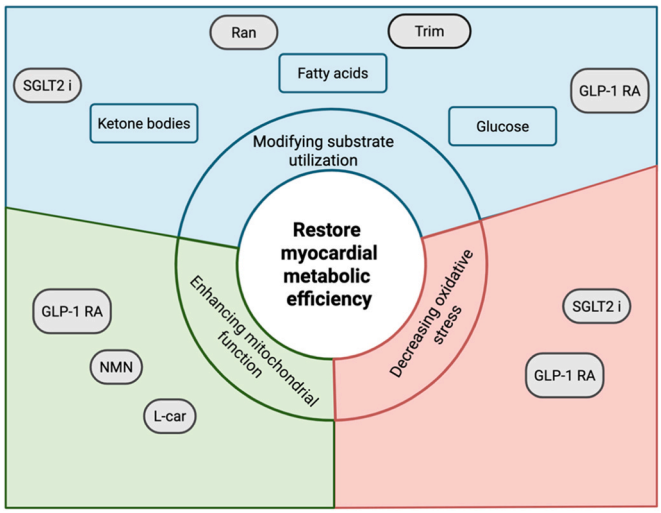

Fig. 3. The main therapeutic targets currently used in HFpEF. The primary therapeutic targets in HFpEF include modifying substrate utilization, enhancing mitochondrial function, and decreasing oxidative stress to restore myocardial metabolic efficiency. Sodium-glucose cotransporter 2 inhibitors (SGLT2i) moderately induce ketogenesis, shifting substrate utilization toward ketone bodies, which are efficient fuels by reducing oxygen consumption for ATP production and supporting mitochondrial function. In addition to modest metabolic modulation, their mechanism of benefit in HFpEF likely involves a combination of mild diuresis, natriuresis, preload and afterload reduction, as well as anti-inflammatory effects. GLP-1 receptor agonists (GLP-1 RA) improve glucose utilization, fatty acid oxidation, and mitochondrial function, especially in patients with obesity or insulin resistance. They also target endothelial function, enhance nitric oxide availability, and improve microvascular perfusion, which can be compromised in HFpEF, while reducing systemic inflammatory signaling linked to visceral adipose tissue. Ranolazine (Ran) and Trimetazidine (Trim) partially inhibit fatty acid oxidation, promoting a shift toward glucose oxidation, which requires less oxygen per ATP molecule. L-carnitine (L-car) supplementation enhances diastolic and systolic function in hemodialysis patients by improving energy metabolism and facilitating the transport of long-chain fatty acids to the mitochondria. Nicotinamide riboside (NMN) boosts NAD+ levels, improving mitochondrial respiration and reducing myocardial fibrosis. GLP-1 RA: Glucagon-Like Peptide-1 receptor agonists, NMN: Nicotinamide riboside, Ran: Ranolazine, SGLT2i: Sodium-glucose cotransporter 2 inhibitors, Trim: Trimetazidine, L-car: L-carnitine.

GLP-1RAs may improve nitric oxide availability and microvascular perfusion, which are often impaired in HFpEF [89]. The STEP-HFpEF trial reported that semaglutide improved symptoms, exercise tolerance, and cardiac biomarkers in patients with HFpEF and obesity. These improvements were accompanied by reductions in systemic inflammation, as measured by high-sensitivity CRP [90]. Further studies are needed to determine their long-term impact on cardiac structure and clinical outcomes across diverse HFpEF populations.

Sodium-glucose cotransporter-2 inhibitors (SGLT2is) have emerged as a leading therapeutic class for HFpEF. Initially developed for glycemic control in type 2 diabetes, SGLT2is like dapagliflozin and empagliflozin have demonstrated cardiovascular benefits across many patients, including those without diabetes [94–96].

In HFpEF, SGLT2is are believed to exert part of their benefit through metabolic reprogramming. These agents mildly induce ketogenesis, shift substrate utilization toward ketone bodies, and improve cardiac energetics. Ketone bodies, particularly βOHB, are efficient fuels that reduce oxygen consumption per ATP produced and support mitochondrial function by activating enzymes like citrate synthase and reducing protein acetylation [97].

However, the extent to which SGLT2is increase ketone levels in HFpEF is debated. In the PRESERVED-HF trial, targeted metabolomic profiling of dapagliflozin showed no significant increase in circulating ketone concentrations, a result echoed in EMPA-VISION. These findings suggest that, unlike in HFrEF or diabetes, the ketone-related effects of SGLT2is may not be central in HFpEF [98,99]. Despite this, SGLT2is have been consistently shown to improve functional status, quality of life, and hospitalization rates in HFpEF patients. Their mechanism of benefit likely involves a combination of mild diuresis, natriuresis, reduced preload/afterload, and anti-inflammatory effects alongside modest metabolic modulation.

7. Future perspectives and limitations

AI is revolutionizing disease management by facilitating precision medicine through predictive analytics, risk stratification, and treatment optimization. AI encompasses various technologies that simulate human intelligence computationally. ML, a subset of AI, utilizes mathematical frameworks to identify patterns in data and make predictions [100]. DL is an evolution of ML that uses large-scale artificial neural networks to automatically extract features from raw data through a multilayer architecture, in contrast to traditional ML methods like Random Forest, which require manually engineered features. By combining phenotypic and multi-omics data, ML and DL algorithms can identify pathophysiological mechanisms and enhance risk prediction, facilitating personalized care. They also reflect changes in the body in response to treatments, allowing timely adjustments to therapy [101]. These techniques are commonly applied to diagnose and manage non-communicable diseases, such as CVD and cardiometabolic diseases [102–104]. Integrating multi-omics data using ML models has enhanced the risk prediction of CVD and HF, surpassing the predictive accuracy of traditional clinical risk scores, which are limited at the individual level. These techniques have highlighted complex associations and nonlinear interactions that traditional methods may overlook. [105–109]. Furthermore, DL algorithms are used to automate the assessment of echocardiograms, cardiac MRI, and CT scans in HF.

The evidence gathered so far, although preliminary and based on preclinical or exploratory clinical studies, suggests a promising future. The integration of ML and DL with comprehensive multi-omic analysis has the potential to provide a multidimensional understanding of HFpEF. AI integrated with a multi-omics approach has the potential to address the complex and heterogeneous nature of HFpEF with important implications for critical issues such as early diagnosis, identifying personalized treatments, and discontinuing ineffective therapies. Moreover, it offers a reassuring potential to reduce overall healthcare costs [110–114].

Although their application has increased significantly, AI and ML techniques still present several limitations. The primary challenges include some important methodological issues, such as the volume and lack of standardization of omics data, the diversity of collected samples, technical artifacts like batch effects that occur during sequencing, and the integration of multi-omics data. Although the volume of omics data in public databases is rapidly increasing due to advances in data collection methods, their use faces challenges related to the lack of standardized methods for data collection and pre-processing. Furthermore, the integration of data from different omics platforms can generate biases that compromise the effectiveness of the analysis [101, 108]. Prospectively, it will therefore be essential to identify precise methodologies to counteract the high dimensionality and heterogeneity of the data and evaluate the accuracy and reproducibility of the model across different biobank datasets [115–119]. Another important limitation relates to translational considerations. The integration of multi-omics into clinical practice will increasingly require a multidisciplinary approach to interpreting complex data. Translational research, which serves as a bridge to clinical application, will be crucial in this process [112]. Preclinical models enable controlled studies of genetic and environmental variables; however, translating findings to humans can be challenging due to the genetic complexity and environmental diversity [115]. As a result, advancements in technology will necessitate

substantial efforts in translational research to integrate these new techniques into clinical practice effectively [120]. Finally, the application of AI and MI models requires rigorous ethical considerations. The unethical collection of omics data can lead to biased results based on gender and race, or to the violation of privacy protection protocols [121–124]. Therefore, it is crucial to establish regulatory and societal standards that explicitly include and protect privacy. It will be essential to optimize benefits while minimizing associated risks, and it is a responsibility that the scientific community must uphold.

8. Conclusion

The intricate pathophysiology of HFpEF is significantly influenced by myocardial metabolic changes, particularly mitochondrial dysfunction and metabolic inflexibility. Delving into these complexities through multi-omics holds promise for unraveling the biological processes that contribute to the development of HFpEF. Emerging evidence highlights the potential of multi-omics to identify innovative biomarkers and therapeutic targets, paving the way for exciting new avenues in research and the pursuit of personalized treatment strategies. However, to fully harness the potential of AI and ML, combined with multi-omics, in the management of HFpEF and to ensure that personalized and accessible care becomes a reality for all patients, it is essential to address and overcome current limitations. This task is a central focus of ongoing research and development efforts, guiding us toward a future where targeted therapies can make a significant difference.

CRediT authorship contribution statement

Massimo Federici: Writing – review & editing, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization. **Fernández-Real Jose Manuel:** Writing – review & editing, Supervision. **Rossella Menghini:** Writing – review & editing, Supervision, Methodology. **Eugenio Martelli:** Writing – review & editing, Supervision. **Loredana Bucciarelli:** Writing – review & editing, Supervision. **Viviana Casagrande:** Writing – review & editing, Supervision, Methodology. **Rocco Mollace:** Writing – review & editing, Writing – original draft, Investigation, Data curation. **Susanna Longo:** Writing – review & editing, Writing – original draft, Visualization, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

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Declaration of Competing Interest

All the authors declare that they have no significant conflicts of interest between them and with the work.

Data availability

Data supporting this review were obtained from publicly available sources

References

[1] K. Teramoto, T.K. Teng, C. Chandramouli, J. Tromp, Y. Sakata, C.S. Lam, Epidemiology and clinical features of heart failure with preserved ejection fraction, Card. Fail Rev. 8 (2022 Aug 4) e27, https://doi.org/10.15420/cfr.2022.06.
[2] S.M. Dunlay, V.L. Roger, M.M. Redfield, Epidemiology of heart failure with preserved ejection fraction, Nat. Rev. Cardiol. 14 (10) (2017 Oct) 591–602, https://doi.org/10.1038/nrcardio.2017.65.
[3] L.A. Shehadeh, E. Robleto, G.D. Lopaschuk, Cardiac energy substrate utilization in heart failure with preserved ejection fraction: reconciling conflicting evidence on fatty acid and glucose metabolism, Am. J. Physiol. Heart Circ. Physiol. 328 (6) (2025 Jun 1) H1267–H1295, https://doi.org/10.1152/ajpheart.00121.2025.
[4] R. Rasalam, A. Sindone, G. Deed, R.G. Audehm, J.J. Atherton, State of precision medicine for heart failure with preserved ejection fraction in a new therapeutic age, ESC Heart Fail 12 (3) (2025 Jun) 1544–1557, https://doi.org/10.1002/ehf2.15205.
[5] S. Longo, R. Menghini, M. Federici, Gut Microbiota and Type 2 Diabetes Mellitus, in: M. Federici, R. Menghini (Eds.), Gut Microbiome, Microbial Metabolites and Cardiometabolic Risk. Endocrinology, Springer, Cham, 2023, https://doi.org/10.1007/978-3-031-08115-6_8-1.
[6] D.W. Kitzman, B. Upadhya, S. Vasu, What the dead can teach the living: systemic nature of heart failure with preserved ejection fraction, Circulation 131 (6) (2015 Feb 10) 522–524, https://doi.org/10.1161/CIRCULATIONAHA.114.014420.
[7] K. Wegermann, M. Fudim, R. Henao, C.F. Howe, R. McGarrah, C. Guy, M. F. Abdelmalek, A.M. Diehl, C.A. Moylan, Serum metabolites are associated with HFpEF in biopsy-proven nonalcoholic fatty liver disease, J. Am. Heart Assoc. 12 (14) (2023 Jul 18) e029873, https://doi.org/10.1161/JAHA.123.029873.
[8] A.C. Pouleur, N. Menghoum, J. Cumps, A. Marino, M. Badii, S. Lejeune, J. T. Legault, G. Boucher, D. Gruson, C. Roy, S. Battault, L. Mahrouche, V. Pedneault-Gagnon, D. Charpentier, A. Furtos, J. Hussin, D. Rhainds, J. C. Tardif, L. Bertrand, C.D. Rosiers, S. Horman, C. Beauloye, Plasma myo-inositol elevation in heart failure: clinical implications and prognostic significance. Results from the Belgian and Canadian metabolomics in HFpEF (BECAME-HF) research project, EBioMedicine 107 (2024 Sep) 105264, https://doi.org/10.1016/j.ebiom.2024.105264.
[9] K.L. Culler, A. Sinha, M. Filipp, P. Giro, N.B. Allen, K.D. Taylor, X. Guo, E. Thorp, B.H. Freed, P. Greenland, W.S. Post, A. Bertoni, D. Herrington, C. Gao, Y. Wang, S.J. Shah, R.B. Patel, Metabolomic profiling identifies novel metabolites associated with cardiac dysfunction, Sci. Rep. 14 (1) (2024 Sep 5) 20694, https://doi.org/10.1038/s41598-024-71329-y.
[10] M. Saddik, G.D. Lopaschuk, Myocardial triglyceride turnover and contribution to energy substrate utilization in isolated working rat hearts, J. Biol. Chem. 266 (13) (1991 May 5) 8162–8170.
[11] S. Neubauer, The failing heart–an engine out of fuel, N. Engl. J. Med. 356 (11) (2007 Mar 15) 1140–1151, https://doi.org/10.1056/NEJMra063052.
[12] H. Liu, S. Wang, J. Wang, X. Guo, Y. Song, K. Fu, Z. Gao, D. Liu, W. He, L.L. Yang, Energy metabolism in health and diseases, Signal Transduct. Target Ther. 10 (1) (2025 Feb 18) 69, https://doi.org/10.1038/s41392-025-02141-x.
[13] G.D. Lopaschuk, Q.G. Karwi, R. Tian, A.R. Wende, E.D. Abel, Cardiac energy metabolism in heart failure, Circ. Res. 128 (10) (2021 May 14) 1487–1513, https://doi.org/10.1161/CIRCRESAHA.121.318241.
[14] 11 Murthy M.S. Pande, SV. Malonyl-CoA binding site and the overt carnitine palmitoyltransferase activity reside on the opposite sides of the outer mitochondrial membrane, Proc. Natl. Acad. Sci. 84 (2) (1987 Jan) 378–382, https://doi.org/10.1073/pnas.84.2.378.
[15] 12 Saddik M. Gamble, J. Witters, L.A. Lopaschuk, GD. Acetyl-CoA carboxylase regulation of fatty acid oxidation in the heart, J. Biol. Chem. 268 (34) (1993 Dec 5) 25836–25845.
[16] S. Chen, Y. Zou, C. Song, K. Cao, K. Cai, Y. Wu, Z. Zhang, D. Geng, W. Sun, N. Ouyang, N. Zhang, Z. Li, G. Sun, Y. Zhang, Y. Sun, Y. Zhang, The role of glycolytic metabolic pathways in cardiovascular disease and potential therapeutic approaches, Basic Res. Cardiol. 118 (1) (2023 Nov 8) 48, https://doi.org/10.1007/s00395-023-01018-w.
[17] C. Dai, Q. Li, H.I. May, C. Li, G. Zhang, G. Sharma, A.D. Sherry, C.R. Malloy, C. Khemtong, Y. Zhang, Y. Deng, T.G. Gillette, J. Xu, D.T. Scadden, Z.V. Wang, Lactate dehydrogenase a governs cardiac hypertrophic growth in response to hemodynamic stress, Cell Rep. 32 (9) (2020 Sep 1) 108087, https://doi.org/10.1016/j.celrep.2020.108087.
[18] K.L. Ho, Q.G. Karwi, C. Wagg, L. Zhang, K. Vo, T. Altamimi, G.M. Uddin, J. R. Ussher, G.D. Lopaschuk, Ketones can become the major fuel source for the heart but do not increase cardiac efficiency, Cardiovasc. Res. 117 (4) (2021 Mar 21) 1178–1187, https://doi.org/10.1093/cvr/cvaa143.
[19] Q.G. Karwi, G.D. Lopaschuk, Branched-chain amino acid metabolism in the failing heart, Cardiovasc Drugs Ther. 37 (2) (2023 Apr) 413–420, https://doi.org/10.1007/s10557-022-07320-4.
[20] T. Doenst, T.D. Nguyen, E.D. Abel, Cardiac metabolism in heart failure: implications beyond ATP production, Circ. Res. 113 (6) (2013 Aug 30) 709–724, https://doi.org/10.1161/CIRCRESAHA.113.300376.
[21] M.R. Zile, C.F. Baicu, J.S. Ikonomidis, R.E. Stroud, P.J. Nietert, A.D. Bradshaw, R. Slater, B.M. Palmer, P. Van Buren, M. Meyer, M.M. Redfield, D.A. Bull, H. L. Granzier, M.M. LeWinter, Myocardial stiffness in patients with heart failure and a preserved ejection fraction: contributions of collagen and titin, Circulation 131 (14) (2015 Apr 7) 1247–1259, https://doi.org/10.1161/CIRCULATIONAHA.114.013215.

[22] M. Obokata, Y.N.V. Reddy, B.A. Borlaug, Diastolic dysfunction and heart failure with preserved ejection fraction, Underst. Mech. Using Noninvasive Methods JACC Cardiovasc. Imaging 13 (1 Pt 2) (2020 Jan) 245–257, https://doi.org/10.1016/j.jcmg.2018.12.034.

[23] Y. Zhou, Myocardial structural remodeling in HFpEF: capillary rarefaction and the fibrotic response, J. Clin. Med. 9 (3) (2020) 715, https://doi.org/10.3390/jcm9030715.

[24] S.F. Mohammed, S. Hussain, S.A. Mirzoyev, W.D. Edwards, J.J. Maleszewski, M. M. Redfield, Coronary microvascular rarefaction and myocardial fibrosis in heart failure with preserved ejection fraction, Circulation 131 (6) (2015 Feb 10) 550–559, https://doi.org/10.1161/CIRCULATIONAHA.114.009625.

[25] X. Lin, G. Wu, S. Wang, J. Huang, The prevalence of coronary microvascular dysfunction (CMD) in heart failure with preserved ejection fraction (HFpEF): a systematic review and meta-analysis, Heart Fail Rev. 29 (2) (2024 Mar) 405–416, https://doi.org/10.1007/s10741-023-10362-x.

[26] M.R. Zile, C.F. Baicu, W.H. Gaasch, Diastolic heart failure–abnormalities in active relaxation and passive stiffness of the left ventricle, N. Engl. J. Med. 350 (19) (2004 May 6) 1953–1959, https://doi.org/10.1056/NEJMoa032566.

[27] J.A. Henry, L.S. Couch, O.J. Rider, Myocardial metabolism in heart failure with preserved ejection fraction, J. Clin. Med. 13 (5) (2024 Feb 20) 1195, https://doi.org/10.3390/jcm13051195.

[28] C.E. Molina, Diastolic dysfunction in heart failure with preserved ejection fraction: role of phospholamban and calcium cycling proteins, Eur. Heart J. 37 (5) (2016) 397–407, https://doi.org/10.1093/eurheartj/ehv603.

[29] O. Sorop, Mitochondrial abnormalities drive diastolic dysfunction in HFpEF, Front. Physiol. 13 (2022) 847379, https://doi.org/10.3389/fphys.2022.847379.

[30] K. Sharma, Mitochondrial dysfunction in HFpEF: bioenergetic impairment and oxidative stress, J. Clin. Med. 9 (1) (2020) 243, https://doi.org/10.3390/jcm9010243.

[31] A.J. Murray, Energetics of failing hearts: evidence from phosphorus-31 magnetic resonance spectroscopy, Circ. Res. 124 (1) (2019) 120–132, https://doi.org/10.1161/CIRCRESAHA.118.313786.

[32] S. Gao, X.P. Liu, T.T. Li, L. Chen, Y.P. Feng, Y.K. Wang, Y.J. Yin, P.J. Little, X. Q. Wu, S.W. Xu, X.D. Jiang, Animal models of heart failure with preserved ejection fraction (HFpEF): from metabolic pathobiology to drug discovery, Acta Pharm. Sin. 45 (1) (2024 Jan) 23–35, https://doi.org/10.1038/s41401-023-01152-0.

[33] J. Buchanan, P.K. Mazumder, P. Hu, G. Chakrabarti, M.W. Roberts, U.J. Yun, R. C. Cooksey, S.E. Litwin, E.D. Abel, Reduced cardiac efficiency and altered substrate metabolism precedes the onset of hyperglycemia and contractile dysfunction in two mouse models of insulin resistance and obesity, Endocrinology 146 (12) (2005 Dec) 5341–5349, https://doi.org/10.1210/en.2005-0938.

[34] J.C. Chatham, Seymour AM. Cardiac carbohydrate metabolism in Zucker diabetic fatty rats, Cardiovasc Res. 55 (1) (2002 Jul) 104–112, https://doi.org/10.1016/s0008-6363(02)00399-1.

[35] L.S. Mansor, E.R. Gonzalez, M.A. Cole, D.J. Tyler, J.H. Beeson, K. Clarke, C. A. Carr, L.C. Heather, Cardiac metabolism in a new rat model of type 2 diabetes using high-fat diet with low dose streptozotocin, Cardiovasc. Diabetol. 12 (2013 Sep 24) 136, https://doi.org/10.1186/1475-2840-12-136.

[36] D. Murashige, C. Jang, M. Neinast, J.J. Edwards, A. Cowan, M.C. Hyman, J. D. Rabinowitz, D.S. Frankel, Z. Arany, Comprehensive quantification of fuel use by the failing and nonfailing human heart, Science 370 (6514) (2020 Oct 16) 364–368, https://doi.org/10.1126/science.abc8861.

[37] B.A. Borlaug, W.J. Paulus, Heart failure with preserved ejection fraction: pathophysiology, diagnosis, and treatment, Eur. Heart J. 32 (6) (2011 Mar) 670–679, https://doi.org/10.1093/eurheartj/ehq426.

[38] V. Ormazabal, S. Nair, O. Elfeky, C. Aguayo, C. Salomon, F.A. Zuñiga, Association between insulin resistance and the development of cardiovascular disease, Cardiovasc. Diabetol. 17 (1) (2018 Aug 31) 122, https://doi.org/10.1186/s12933-018-0762-4.

[39] W.C. Stanley, F.A. Recchia, Lipotoxicity and the development of heart failure: moving from mouse to man, Cell Metab. 12 (6) (2010 Dec 1) 555–556, https://doi.org/10.1016/j.cmet.2010.11.016.

[40] P.C. Schulze, K. Drosatos, I.J. Goldberg, Lipid Use and Misuse by the Heart, Circ. Res 118 (11) (2016 May 27) 1736–1751, https://doi.org/10.1161/CIRCRESAHA.116.306842.

[41] L.M. Le Page, O.J. Rider, A.J. Lewis, V. Ball, K. Clarke, E. Johansson, C.A. Carr, L. C. Heather, D.J. Tyler, Increasing Pyruvate Dehydrogenase Flux as a Treatment for Diabetic Cardiomyopathy: A Combined 13C Hyperpolarized Magnetic Resonance and Echocardiography Study, Diabetes 64 (8) (2015 Aug) 2735–2743, https://doi.org/10.2337/db14-1560.

[42] M. Almutairi, K. Gopal, A.A. Greenwell, A. Young, R. Gill, H. Aburasayn, R. Al Batran, J.J. Chahade, M. Gandhi, F. Eaton, R.J. Mailloux, J.R. Ussher, The GLP-1 Receptor Agonist Liraglutide Increases Myocardial Glucose Oxidation Rates via Indirect Mechanisms and Mitigates Experimental Diabetic Cardiomyopathy, Can. J. Cardiol. 37 (1) (2021 Jan) 140–150, https://doi.org/10.1016/j.cjca.2020.02.098.

[43] R. Nielsen, N. Møller, L.C. Gormsen, L.P. Tolbod, N.H. Hansson, J. Sorensen, H. J. Harms, J. Frøkiær, H. Eiskjaer, N.R. Jespersen, S. Mellemkjaer, T.R. Lassen, K. Pryds, H.E. Bøtker, H. Wiggers, Cardiovascular Effects of Treatment With the Ketone Body 3-Hydroxybutyrate in Chronic Heart Failure Patients, Circulation 139 (18) (2019 Apr 30) 2129–2141, https://doi.org/10.1161/CIRCULATIONAHA.118.036459.

[44] P. Puchalska, P.A. Crawford, Metabolic and Signaling Roles of Ketone Bodies in Health and Disease, Annu Rev. Nutr. 41 (2021 Oct 11) 49–77, https://doi.org/10.1146/annurev-nutr-111120-111518.

[45] S. Longo, F. Del Chierico, M. Scanu, F. Toto, J.M. Legramante, S. Rizza, L. Putignani, M. Federici, An Investigation of Metabolic Risk Factors and Gut Microbiota in Unexplained Syncope, Biomedicines 12 (2) (2024 Jan 24) 264, https://doi.org/10.3390/biomedicines12020264.

[46] S. Longo, I. Cicalini, D. Pieragostino, V. De Laurenzi, J.M. Legramante, R. Menghini, S. Rizza, M. Federici, A Metabolomic Approach to Unexplained Syncope, Biomedicines 12 (11) (2024 Nov 19) 2641, https://doi.org/10.3390/biomedicines12112641.

[47] M. Belli, L. Barone, S. Longo, F.R. Prandi, D. Lecis, R. Mollace, D. Margonato, S. Muscoli, D. Sergi, M. Federici, F. Barillà, Gut Microbiota Composition and Cardiovascular Disease: A Potential New Therapeutic Target? Int J. Mol. Sci. 24 (15) (2023 Jul 26) 11971, https://doi.org/10.3390/ijms241511971.

[48] F. Edelmann, R. Wachter, A.G. Schmidt, E. Kraigher-Krainer, C. Colantonio, W. Kamke, A. Duvinage, R. Stahrenberg, K. Durstewitz, M. Löffler, H.D. Düngen, C. Tschöpe, C. Herrmann-Lingen, M. Halle, G. Hasenfuss, G. Gelbrich, B. Pieske, Aldo-DHF Investigators, Effect of spironolactone on diastolic function and exercise capacity in patients with heart failure with preserved ejection fraction: the Aldo-DHF randomized controlled trial, JAMA 309 (8) (2013 Feb 27) 781–791, https://doi.org/10.1001/jama.2013.905.

[49] B. Pitt, M.A. Pfeffer, S.F. Assmann, R. Boineau, I.S. Anand, B. Claggett, N. Clausell, A.S. Desai, R. Diaz, J.L. Fleg, I. Gordeev, B. Harty, J.F. Heitner, C. T. Kenwood, E.F. Lewis, E. O'Meara, J.L. Probstfield, T. Shaburishvili, S.J. Shah, S.D. Solomon, N.K. Sweitzer, S. Yang, S.M. McKinlay, T.O.P.C.A.T. Investigators, Spironolactone for heart failure with preserved ejection fraction, N. Engl. J. Med 370 (15) (2014 Apr 10) 1383–1392, https://doi.org/10.1056/NEJMoa1313731.

[50] M. Abudurexiti, R. Abuduhalike, T. Naman, N. Wupuer, D. Duan, M. Keranmu, A. Mahemuti, Integrated proteomic and metabolomic profiling reveals novel insights on the inflammation and immune response in HFpEF, BMC Genom. 25 (1) (2024 Jul 8) 676, https://doi.org/10.1186/s12864-024-10575-w.

[51] L. Lai, T.C. Leone, M.P. Keller, O.J. Martin, A.T. Broman, J. Nigro, K. Kapoor, T. R. Koves, R. Stevens, O.R. Ilkayeva, R.B. Vega, A.D. Attie, D.M. Muoio, D.P. Kelly, Energy metabolic reprogramming in the hypertrophied and early stage failing heart: a multisystems approach, Circ. Heart Fail 7 (6) (2014 Nov) 1022–1031, https://doi.org/10.1161/CIRCHEARTFAILURE.114.001469.

[52] A.A. Gibb, E.K. Murray, D.M. Eaton, A.T. Huynh, D. Tomar, J.F. Garbincius, D. W. Kolmetzky, R.M. Berretta, M. Wallner, S.R. Houser, J.W. Elrod, Molecular Signature of HFpEF, Syst. Biol. a Card. Centr Large Anim. Model. JACC Basic Transl. Sci. 6 (8) (2021 Aug 23) 650–672, https://doi.org/10.1016/j.jacbts.2021.07.004.

[53] X.Y. Gui, S.W. Rabkin, C-Reactive Protein, Interleukin-6, Trimethylamine-N-Oxide, Syndecan-1, Nitric Oxide, and Tumor Necrosis Factor Receptor-1 in Heart Failure with Preserved Versus Reduced Ejection Fraction: a Meta-Analysis, Curr. Heart Fail Rep. 20 (1) (2023 Feb) 1–11, https://doi.org/10.1007/s11897-022-00584-9.

[54] B. Bai, M. Cheng, L. Jiang, J. Xu, H. Chen, Y. Xu, High Neutrophil to Lymphocyte Ratio and Its Gene Signatures Correlate With Diastolic Dysfunction in Heart Failure With Preserved Ejection Fraction, Front Cardiovasc Med 8 (2021 Jun 24) 614757, https://doi.org/10.3389/fcvm.2021.614757.

[55] M.H. Janeiro, M.J. Ramírez, F.I. Milagro, J.A. Martínez, M. Solas, Implication of Trimethylamine N-Oxide (TMAO) in Disease: Potential Biomarker or New Therapeutic Target, Nutrients 10 (10) (2018 Oct 1) 1398, https://doi.org/10.3390/nu10101398.

[56] T. Tanaka, M. Narazaki, T. Kishimoto, IL-6 in inflammation, immunity, and disease, Cold Spring Harb. Perspect. Biol. 6 (10) (2014 Sep 4) a016295, https://doi.org/10.1101/cshperspect.a016295.

[57] J.O. Lundberg, M.T. Gladwin, A. Ahluwalia, N. Benjamin, N.S. Bryan, A. Butler, P. Cabrales, A. Fago, M. Feelisch, P.C. Ford, B.A. Freeman, M. Frenneaux, J. Friedman, M. Kelm, C.G. Kevil, D.B. Kim-Shapiro, A.V. Kozlov, J.R. Lancaster, Jr, D.J. Lefer, K. McColl, K. McCurry, R.P. Patel, J. Petersson, T. Rassaf, V. P. Reutov, G.B. Richter-Addo, A. Schechter, S. Shiva, K. Tsuchiya, E.E. van Faassen, A.J. Webb, B.S. Zuckerbraun, J.L. Zweier, E. Weitzberg, Nitrate and nitrite in biology, nutrition and therapeutics, Nat. Chem. Biol. 5 (12) (2009 Dec) 865–869, https://doi.org/10.1038/nchembio.260.

[58] T. Szatmári, K. Dobra, The role of syndecan-1 in cellular signaling and its effects on heparan sulfate biosynthesis in mesenchymal tumors, Front Oncol. 3 (2013 Dec 19) 310, https://doi.org/10.3389/fonc.2013.00310.

[59] H.T. Idriss, J.H. Naismith, TNF alpha and the TNF receptor superfamily: structure-function relationship(s), Microsc. Res Tech. 50 (3) (2000 Aug 1) 184–195, https://doi.org/10.1002/1097-0029(20000801)50:3<184::AID-JEMT2>3.0.CO;2-H.

[60] ovanovic N. Foryst-Ludwig, A. Klose, C. da Conceicao, C.R. Alasfar, L. Birkner, T. Forslund, S.K. Kintscher, U. Edelmann, F. An altered plasma lipidome-phenome network characterizes heart failure with preserved ejection fraction, ESC Heart Fail 11 (3) (2024 Jun) 1553–1566, https://doi.org/10.1002/ehf2.14654.

[61] S. Dutta, D. Li, A. Wang, M. Ishak, K. Cook, M. Farnham, H. Dissanayake, P. Cistulli, I. Hunyor, R. Liu, I. Wilcox, Y.C. Koay, J. Yang, S. Lal, J.F. O'Sullivan, Metabolite signatures of heart failure, sleep apnoea, their interaction, and outcomes in the community, ESC Heart Fail 8 (6) (2021 Dec) 5392–5402, https://doi.org/10.1002/ehf2.13631.

[62] G. Liu, N.Q.H. Nguyen, K.E. Wong, S.K. Agarwal, E. Boerwinkle, P.P. Chang, B. L. Claggett, L.R. Loehr, J. Ma, K. Matsushita, C.J. Rodriguez, J.S. Rossi, S. D. Russell, R.B. Stacey, A.M. Shah, B. Yu, Metabolomic Association and Risk Prediction With Heart Failure in Older Adults, Circ. Heart Fail 17 (3) (2024 Mar) e010896, https://doi.org/10.1161/CIRCHEARTFAILURE.123.010896.

[63] K. Weiss, M. Schär, G.S. Panjrath, Y. Zhang, K. Sharma, P.A. Bottomley, A. Golozar, A. Steinberg, G. Gerstenblith, S.D. Russell, R.G. Weiss, Fatigability,

Exercise Intolerance, and Abnormal Skeletal Muscle Energetics in Heart Failure, Circ. Heart Fail 10 (7) (2017 Jul) e004129, https://doi.org/10.1161/CIRCHEARTFAILURE.117.004129.
[64] H. Omran, S. Illien, D. MacCarter, St Cyr, J. Lüderitz, B. D-Ribose improves diastolic function and quality of life in congestive heart failure patients: a prospective feasibility study, Eur. J. Heart Fail 5 (5) (2003 Oct) 615–619, https://doi.org/10.1016/s1388-9842(03)00060-6.
[65] R. Mollace, S. Longo, M. Nardin, A. Tavernese, V. Musolino, A. Cardamone, M. Federici, Role of MASLD in CVD: a review of emerging treatment options, Diabetes Res. Clin. Pr. 217 (2024 Nov) 111891, https://doi.org/10.1016/j.diabres.2024.111891.
[66] P. Singh, A. Hoori, J. Freeze, et al., Leveraging calcium score CT radiomics for heart failure risk prediction, Sci. Rep. 14 (1) (2024) 26898, https://doi.org/10.1038/s41598-024-77269-x.
[67] J. Lee, T. Hu, M.C. Williams, et al., Detection of arterial remodeling using epicardial adipose tissue assessment from CT calcium scoring scan, Front Cardiovasc Med 12 (2025) 1543816, https://doi.org/10.3389/fcvm.2025.1543816.
[68] T. Hu, J. Freeze, P. Singh, et al., Artificial Intelligence Prediction of Cardiovascular Events Using Opportunistic Epicardial Adipose Tissue Assessments From Computed Tomography Calcium Score, JACC Adv. 3 (9) (2024) 101188, https://doi.org/10.1016/j.jacadv.2024.101188.
[69] A. Palazzuoli, F. Tramonte, M. Beltrami, Laboratory and Metabolomic Fingerprint in Heart Failure with Preserved Ejection Fraction: From Clinical Classification to Biomarker Signature, 13, Biomolecules 13 (1) (2023 Jan) 173, https://doi.org/10.3390/biom13010173.
[70] V.S. Hahn, C. Petucci, M.S. Kim, K.C. Bedi, Jr, H. Wang, S. Mishra, N. Koleini, E. J. Yoo, K.B. Margulies, Z. Arany, D.P. Kelly, D.A. Kass, K. Sharma, Myocardial Metabolomics of Human Heart Failure With Preserved Ejection Fraction, Circulation 147 (15) (2023 Apr 11) 1147–1161, https://doi.org/10.1161/CIRCULATIONAHA.122.061846.
[71] F. Naeem, T.C. Leone, C. Petucci, C. Shoffler, R.C. Kodihalli, T. Hidalgo, C. Tow-Keogh, J. Mancuso, I. Tzameli, D. Bennett, J.D. Groarke, R.J.R. Flach, D.J. Rader, D.P. Kelly, Targeted Quantitative Plasma Metabolomics Identifies Metabolite Signatures that Distinguish Heart Failure with Reduced and Preserved Ejection Fraction, medRxiv [Prepr.] (2024 Jul 25) 2024.07.24.24310961, https://doi.org/10.1101/2024.07.24.24310961. Update in: ESC Heart Fail. 2025 Apr 15. doi: 10.1002/ehf2.15285.
[72] W.G. Hunter, J.P. Kelly, R.W. McGarrah, 3rd, M.G. Khouri, D. Craig, C. Haynes, O. Ilkayeva, R.D. Stevens, J.R. Bain, M.J. Muehlbauer, C.B. Newgard, G.M. Felker, A.F. Hernandez, E.J. Velazquez, W.E. Kraus, S.H. Shah, Metabolomic Profiling Identifies Novel Circulating Biomarkers of Mitochondrial Dysfunction Differentially Elevated in Heart Failure With Preserved Versus Reduced Ejection Fraction: Evidence for Shared Metabolic Impairments in Clinical Heart Failure, J. Am. Heart Assoc. 5 (8) (2016 Jul 29) e003190, https://doi.org/10.1161/JAHA.115.003190.
[73] B.N. Zordoky, M.M. Sung, J. Ezekowitz, R. Mandal, B. Han, T.C. Bjorndahl, S. Bouatra, T. Anderson, G.Y. Oudit, D.S. Wishart, J.R. Dyck, Alberta HEART. Metabolomic fingerprint of heart failure with preserved ejection fraction, PLoS One 10 (5) (2015 May 26) e0124844, https://doi.org/10.1371/journal.pone.0124844.
[74] D.E. Lanfear, J.J. Gibbs, J. Li, R. She, C. Petucci, J.A. Culver, W.H.W. Tang, Y. M. Pinto, L.K. Williams, H.N. Sabbah, S.J. Gardell, Targeted Metabolomic Profiling of Plasma and Survival in Heart Failure Patients, JACC Heart Fail 5 (11) (2017 Nov) 823–832, https://doi.org/10.1016/j.jchf.2017.07.009.
[75] M. Ruiz, F. Labarthe, A. Fortier, B. Bouchard, J. Thompson Legault, V. Bolduc, O. Rigal, J. Chen, A. Ducharme, P.A. Crawford, J.C. Tardif, C. Des Rosiers, Circulating acylcarnitine profile in human heart failure: a surrogate of fatty acid metabolic dysregulation in mitochondria and beyond, Am. J. Physiol. Heart Circ. Physiol. 313 (4) (2017 Oct 1) H768–H781, https://doi.org/10.1152/ajpheart.00820.2016.
[76] Y.C. Wang, Y.C. Koay, C. Pan, Z. Zhou, W. Tang, J. Wilcox, X.S. Li, A. Zagouras, F. Marques, H. Allayee, F.E. Rey, D.M. Kaye, J.F. O'Sullivan, S.L. Hazen, Y. Cao, A.J. Lusis, Indole-3-Propionic Acid Protects Against Heart Failure With Preserved Ejection Fraction, Circ. Res 134 (4) (2024 Feb 16) 371–389, https://doi.org/10.1161/CIRCRESAHA.123.322381.
[77] Z.V. Wang, J.A. Hill, Protein quality control and metabolism: bidirectional control in the heart, Cell Metab. 21 (2) (2015 Feb 3) 215–226, https://doi.org/10.1016/j.cmet.2015.01.016.
[78] G.G. Schiattarella, F. Altamirano, S.Y. Kim, D. Tong, A. Ferdous, H. Piristine, S. Dasgupta, X. Wang, K.M. French, E. Villalobos, S.B. Spurgin, M. Waldman, N. Jiang, H.I. May, T.M. Hill, Y. Luo, H. Yoo, V.G. Zaha, S. Lavandero, T. G. Gillette, J.A. Hill, Xbp1s-FoxO1 axis governs lipid accumulation and contractile performance in heart failure with preserved ejection fraction, Nat. Commun. 12 (1) (2021 Mar 16) 1684, https://doi.org/10.1038/s41467-021-21931-9.
[79] G.G. Schiattarella, F. Altamirano, D. Tong, K.M. French, E. Villalobos, S.Y. Kim, X. Luo, N. Jiang, H.I. May, Z.V. Wang, T.M. Hill, P.P.A. Mammen, J. Huang, D. I. Lee, V.S. Hahn, K. Sharma, D.A. Kass, S. Lavandero, T.G. Gillette, J.A. Hill, Nitrosative stress drives heart failure with preserved ejection fraction, Nature 568 (7752) (2019 Apr) 351–356, https://doi.org/10.1038/s41586-019-1100-z.
[80] L. Luo, Y. Zuo, L. Dai, Metabolic rewiring and inter-organ crosstalk in diabetic HFpEF, Cardiovasc Diabetol. 24 (1) (2025) 155, https://doi.org/10.1186/s12933-025-02707-7.
[81] A.L. Beale, J.A. O'Donnell, M.E. Nakai, et al., The Gut Microbiome of Heart Failure With Preserved Ejection Fraction, JAHA 10 (13) (2021) e020654, https://doi.org/10.1161/JAHA.120.020654.
[82] Z. Huang, X. Mei, Y. Jiang, T. Chen, Y. Zhou, Gut Microbiota in Heart Failure Patients With Preserved Ejection Fraction (GUMPTION Study), Front Cardiovasc Med 8 (2022) 803744, https://doi.org/10.3389/fcvm.2021.803744.
[83] S.J. Guivala, K.A. Bode, J.G. Okun, et al., Interactions between the gut microbiome, associated metabolites and the manifestation and progression of heart failure with preserved ejection fraction in ZSF1 rats, Cardiovasc Diabetol. 23 (1) (2024) 299, https://doi.org/10.1186/s12933-024-02398-6.
[84] A. Salzano, M.Z. Israr, Y. Yazaki, et al., Combined use of trimethylamine N-oxide with BNP for risk stratification in heart failure with preserved ejection fraction: findings from the DIAMONDHFpEF study, Eur. J. Prev. Cardiol. 27 (19) (2020) 2159–2162, https://doi.org/10.1177/2047487319870355.
[85] Y. Kinugasa, K. Nakamura, H. Kamitani, et al., Trimethylamine N-oxide and outcomes in patients hospitalized with acute heart failure and preserved ejection fraction, ESC Heart Fail. 8 (3) (2021) 2103–2110, https://doi.org/10.1002/ehf2.13290.
[86] S. Williams, M. Pourrier, D. McAfee, S. Lin, D. Fedida, Ranolazine improves diastolic function in spontaneously hypertensive rats, Am. J. Physiol. Heart Circ. Physiol. 306 (6) (2014 Mar) H867–H881, https://doi.org/10.1152/ajpheart.00704.2013.
[87] H. Serag, L.E. Wakeel, V. William, M. Abdelsalam, A. Abdelsalam, R. Sayed, Effect of trimetazidine on left ventricular functions and cardiac biomarkers in diabetic patients with left ventricular diastolic dysfunction: a randomized controlled trial, Sci. Rep. 15 (1) (2025 Jan 16) 2115, https://doi.org/10.1038/s41598-024-83213-w.
[88] J. Naito, H. Ohashi, M. Ohno, M. Sugiyama, K. Hayakawa, A. Kunishima, N. Takada, T. Kariya, K. Goto, H. Takatsu, T. Ohira, K. Nakahara, I. Murata, S. Minatoguchi, G. Yoshida, H. Okura, S. Minatoguchi, Long-term levocarnitine ameliorates left ventricular diastolic as well as systolic dysfunction in hemodialysis patients - multi-center study, Circ. Rep. 1 (11) (2019 Oct 11) 508–516, https://doi.org/10.1253/circrep.CR-19-0075.
[89] S. Yamamura, Y. Izumiya, S. Araki, T. Nakamura, Y. Kimura, S. Hanatani, T. Yamada, T. Ishida, M. Yamamoto, Y. Onoue, Y. Arima, E. Yamamoto, Y. Sunagawa, T. Yoshizawa, N. Nakagata, E. Bober, T. Braun, K. Sakamoto, K. Kaikita, T. Morimoto, K. Yamagata, K. Tsujita, Cardiomyocyte Sirt (Sirtuin) 7 Ameliorates stress-induced cardiac hypertrophy by interacting with and deacetylating GATA4, Hypertension 75 (1) (2020 Jan) 98–108, https://doi.org/10.1161/HYPERTENSIONAHA.119.13357.
[90] Y.L. Ma, C.Y. Kong, Z. Guo, M.Y. Wang, P. Wang, F.Y. Liu, D. Yang, Z. Yang, Q. Z. Tang, Semaglutide ameliorates cardiac remodeling in male mice by optimizing energy substrate utilization through the Creb5/NR4a1 axis, Nat. Commun. 15 (1) (2024 Jun 4) 4757, https://doi.org/10.1038/s41467-024-48970-2.
[91] G. Bendotti, L. Montefusco, M.E. Lunati, V. Usuelli, I. Pastore, E. Lazzaroni, E. Assi, A.J. Seelam, B. El Essawy, J. Jang, C. Loretelli, F. D'Addio, C. Berra, M. Ben Nasr, G. Zuccotti, P. Fiorina, The anti-inflammatory and immunological properties of GLP-1 receptor agonists, Pharm. Res 182 (2022 Aug) 106320, https://doi.org/10.1016/j.phrs.2022.106320.
[92] R. Menghini, V. Casagrande, S. Rizza, M. Federici, GLP-1RAs and cardiovascular disease: is the endothelium a relevant platform? Acta Diabetol. 60 (11) (2023 Nov) 1441–1448, https://doi.org/10.1007/s00592-023-02124-w.
[93] M.N. Kosiborod, S.Z. Abildstrøm, B.A. Borlaug, J. Butler, S. Rasmussen, M. Davies, G.K. Hovingh, D.W. Kitzman, M.L. Lindegaard, D.V. Møller, S.J. Shah, M.B. Treppendahl, S. Verma, W. Abhayaratna, F.Z. Ahmed, V. Chopra, J. Ezekowitz, M. Fu, H. Ito, M. Lelonek, V. Melenovsky, B. Merkely, J. Núñez, E. Perna, M. Schou, M. Senni, K. Sharma, P. Van der Meer, D. von Lewinski, D. Wolf, M.C. Petrie, STEP-HFpEF trial committees and investigators. Semaglutide in patients with heart failure with preserved ejection fraction and obesity, N. Engl. J. Med. 389 (12) (2023 Sep 21) 1069–1084, https://doi.org/10.1056/NEJMoa2306963.
[94] J.J.V. McMurray, S.D. Solomon, S.E. Inzucchi, L. Køber, M.N. Kosiborod, F. A. Martinez, P. Ponikowski, M.S. Sabatine, I.S. Anand, J. Bělohlávek, M. Böhm, C. E. Chiang, V.K. Chopra, R.A. de Boer, A.S. Desai, M. Diez, J. Drozdz, A. Dukát, J. Ge, J.G. Howlett, T. Katova, M. Kitakaze, C.E.A. Ljungman, B. Merkely, J. C. Nicolau, E. O'Meara, M.C. Petrie, P.N. Vinh, M. Schou, S. Tereshchenko, S. Verma, C. Held, D.L. DeMets, K.F. Docherty, P.S. Jhund, O. Bengtsson, M. Sjöstrand, A.M. Langkilde, DAPA-HF trial committees and investigators. dapagliflozin in patients with heart failure and reduced ejection fraction, N. Engl. J. Med. 381 (21) (2019 Nov 21) 1995–2008, https://doi.org/10.1056/NEJMoa1911303.
[95] S.D. Anker, J. Butler, G. Filippatos, J.P. Ferreira, E. Bocchi, M. Böhm, Rocca H. P. Brunner-La, D.J. Choi, V. Chopra, E. Chuquiure-Valenzuela, N. Giannetti, J. E. Gomez-Mesa, S. Janssens, J.L. Januzzi, J.R. Gonzalez-Juanatey, B. Merkely, S. J. Nicholls, S.V. Perrone, I.L. Piña, P. Ponikowski, M. Senni, D. Sim, J. Spinar, I. Squire, S. Taddei, H. Tsutsui, S. Verma, D. Vinereanu, J. Zhang, P. Carson, C.S. P. Lam, N. Marx, C. Zeller, N. Sattar, W. Jamal, S. Schnaidt, J.M. Schnee, M. Brueckmann, S.J. Pocock, F. Zannad, M. Packer, EMPEROR-preserved trial investigators. empagliflozin in heart failure with a preserved ejection fraction, N. Engl. J. Med. 385 (16) (2021 Oct 14) 1451–1461, https://doi.org/10.1056/NEJMoa2107038.
[96] C.G. Santos-Gallego, A.P. Vargas-Delgado, J.A. Requena-Ibanez, A. Garcia-Ropero, D. Mancini, S. Pinney, F. Macaluso, S. Sartori, M. Roque, F. Sabatel-Perez, A. Rodriguez-Cordero, M.U. Zafar, I. Fergus, F. Atallah-Lajam, J. P. Contreras, C. Varley, P.R. Moreno, V.M. Abascal, A. Lala, R. Tamler, J. Sanz, V. Fuster, J.J. Badimon, EMPA-TROPISM (ATRU-4) investigators. randomized

trial of empagliflozin in nondiabetic patients with heart failure and reduced ejection fraction, J. Am. Coll. Cardiol. 77 (3) (2021 Jan 26) 243–255, https://doi.org/10.1016/j.jacc.2020.11.008.
[97] R. Pietschner, J. Kolwelter, A. Bosch, K. Striepe, S. Jung, D. Kannenkeril, C. Ott, M. Schiffer, S. Achenbach, R.E. Schmieder, Effect of empagliflozin on ketone bodies in patients with stable chronic heart failure, Cardiovasc Diabetol. 20 (1) (2021 Nov 9) 219, https://doi.org/10.1186/s12933-021-01410-7.
[98] M.E. Nassif, S.L. Windsor, B.A. Borlaug, D.W. Kitzman, S.J. Shah, F. Tang, Y. Khariton, A.O. Malik, T. Khumri, G. Umpierrez, S. Lamba, K. Sharma, S. S. Khan, L. Chandra, R.A. Gordon, J.J. Ryan, S.P. Chaudhry, S.M. Joseph, C. H. Chow, M.K. Kanwar, M. Pursley, E.S. Siraj, G.D. Lewis, B.S. Clemson, M. Fong, M.N. Kosiborod, The SGLT2 inhibitor dapagliflozin in heart failure with preserved ejection fraction: a multicenter randomized trial, Nat. Med. 27 (11) (2021 Nov) 1954–1960, https://doi.org/10.1038/s41591-021-01536-x.
[99] M.J. Hundertmark, A. Adler, C. Antoniades, R. Coleman, J.L. Griffin, R. R. Holman, H. Lamlum, J. Lee, D. Massey, J.J.J.J. Miller, J.E. Milton, S. Monga, F. E. Mózes, A. Nazeer, B. Raman, O. Rider, C.T. Rodgers, L. Valkovič, E. Wicks, M. Mahmod, S. Neubauer, Assessment of cardiac energy metabolism, function, and physiology in patients with heart failure taking empagliflozin: the randomized, controlled EMPA-VISION trial, Circulation 147 (22) (2023 May 30) 1654–1669, https://doi.org/10.1161/CIRCULATIONAHA.122.062021.
[100] S. Vadapalli, H. Abdelhalim, S. Zeeshan, Z. Ahmed, Artificial intelligence and machine learning approaches using gene expression and variant data for personalized medicine, Brief. Bioinform. 23 (5) (2022 Sep 20) bbac191, https://doi.org/10.1093/bib/bbac191.
[101] M. Lin, J. Guo, Z. Gu, W. Tang, H. Tao, S. You, D. Jia, Y. Sun, P. Jia, Machine learning and multi-omics integration: advancing cardiovascular translational research and clinical practice, J. Transl. Med. 23 (1) (2025 Apr 2) 388, https://doi.org/10.1186/s12967-025-06425-2.
[102] J. He, S.L. Baxter, J. Xu, J. Xu, X. Zhou, K. Zhang, The practical implementation of artificial intelligence technologies in medicine, Nat. Med 25 (1) (2019 Jan) 30–36, https://doi.org/10.1038/s41591-018-0307-0.
[103] S.C. Mackenzie, C.A.R. Sainsbury, D.J. Wake, Diabetes and artificial intelligence beyond the closed loop: a review of the landscape, promise and challenges, Diabetologia 67 (2) (2024 Feb) 223–235, https://doi.org/10.1007/s00125-023-06038-8.
[104] W.K. Chung, K. Erion, J.C. Florez, A.T. Hattersley, M.F. Hivert, C.G. Lee, M. I. McCarthy, J.J. Nolan, J.M. Norris, E.R. Pearson, L. Philipson, A.T. McElvaine, W.T. Cefalu, S.S. Rich, P.W. Franks, Precision medicine in diabetes: a consensus report from the American diabetes association (ADA) and the European association for the study of diabetes (EASD), Diabetologia 63 (9) (2020 Sep) 1671–1693, https://doi.org/10.1007/s00125-020-05181-w.
[105] A. Joshi, M. Rienks, K. Theofilatos, M. Mayr, Systems biology in cardiovascular disease: a multiomics approach, Nat. Rev. Cardiol. 18 (5) (2021 May) 313–330, https://doi.org/10.1038/s41569-020-00477-1.
[106] C. Chen, J. Wang, D. Pan, X. Wang, Y. Xu, Yan j, Wang l, Yang x, Yang m, G.-P. Liu, Applications of multi-omics analysis in human diseases, MedComm 4 (2023) e315, https://doi.org/10.1002/mco2.315.
[107] S. Rizza, M. Copetti, M. Cardellini, R. Menghini, C. Pecchioli, A. Luzi, G. Di Cola, O. Porzio, A. Ippoliti, F. Romeo, F. Pellegrini, M. Federici, A score including ADAM17 substrates correlates to recurring cardiovascular event in subjects with atherosclerosis, Atherosclerosis 239 (2) (2015 Apr) 459–464, https://doi.org/10.1016/j.atherosclerosis.2015.01.029.
[108] J. Wang, Z. Kang, Y. Liu, Z. Li, Y. Liu, J. Liu, Identification of immune cell infiltration and diagnostic biomarkers in unstable atherosclerotic plaques by integrated bioinformatics analysis and machine learning, Front Immunol. 13 (2022 Sep 23) 956078, https://doi.org/10.3389/fimmu.2022.956078.
[109] M. Marcinkiewicz-Siemion, M. Kaminski, M. Ciborowski, K. Ptaszynska-Kopczynska, A. Szpakowicz, A. Lisowska, M. Jasiewicz, E. Tarasiuk, A. Kretowski, B. Sobkowicz, K.A. Kaminski, Machine-learning facilitates selection of a novel diagnostic panel of metabolites for the detection of heart failure, 10, Sci. Rep. 10 (1) (2020 Jan) 130, https://doi.org/10.1038/s41598-019-56889-8.
[110] E.C. Palaparthi, T. Padala, R. Singamaneni, R. Manaswini, A. Kantula, P. Aditya Reddy, P. Chandini, A. Sathwika Eliana, P. Siri Samhita, P.K. Patnaik, Emerging therapeutic strategies for heart failure: a comprehensive review of novel pharmacological and molecular targets, Cureus 17 (4) (2025 Apr 1) e81573, https://doi.org/10.7759/cureus.81573.
[111] Y. Luo, F.S. Ahmad, S.J. Shah, Tensor factorization for precision medicine in heart failure with preserved ejection fraction, J. Cardiovasc Transl. Res. 10 (3) (2017 Jun) 305–312, https://doi.org/10.1007/s12265-016-9727-8.
[112] J.M. Bastos, B. Colaço, R. Baptista, C. Gavina, R. Vitorino, Innovations in heart failure management: the role of cutting-edge biomarkers and multi-omics integration, J. Mol. Cell Cardiol. 11 (2025 Mar 1) 100290, https://doi.org/10.1016/j.jmccpl.2025.100290.
[113] M. Ramezani, A. Takian, A. Bakhtiari, H.R. Rabiee, A.A. Fazaeli, S. Sazgarnejad, The application of artificial intelligence in health financing: a scoping review, Cost. Eff. Resour. Alloc. 21 (1) (2023 Nov 6) 83, https://doi.org/10.1186/s12962-023-00492-2.
[114] J. Gomez Rossi, N. Rojas-Perilla, J. Krois, F. Schwendicke, Cost-effectiveness of artificial intelligence as a decision-support system applied to the detection and grading of melanoma, dental caries, and diabetic retinopathy, JAMA Netw. Open 5 (3) (2022 Mar 1) e220269, https://doi.org/10.1001/jamanetworkopen.2022.0269.
[115] R. Alemu, N.T. Sharew, Y.Y. Arsano, M. Ahmed, F. Tekola-Ayele, T.B. Mersha, A. T. Amare, Multi-omics approaches for understanding gene-environment interactions in noncommunicable diseases: techniques, translation, and equity issues, Hum. Genom. 19 (1) (2025 Jan 31) 8, https://doi.org/10.1186/s40246-025-00718-9.
[116] H. Liu, Y. Zhang, Y. Zhao, Y. Li, X. Zhang, L. Bao, R. Yan, Y. Yang, H. Zhou, J. Zhang, S. Song, Research progress and clinical translation potential of coronary atherosclerosis diagnostic markers from a genomic perspective, Genes 16 (1) (2025 Jan 18) 98, https://doi.org/10.3390/genes16010098.
[117] T. Baltrusaitis, C. Ahuja, L.P. Morency, Multimodal machine learning: a survey and taxonomy, IEEE Trans. Pattern Anal. Mach. Intell. 41 (2) (2019 Feb) 423–443, https://doi.org/10.1109/TPAMI.2018.2798607.
[118] M.B. Lopes, R. Coletti, F. Duranton, G. Glorieux, M.A. Jaimes Campos, J. Klein, M. Ley, P. Perco, A. Sampri, A. Tur-Sinai, The omics-driven machine learning path to cost-effective precision medicine in chronic kidney disease, Proteomics 25 (11-12) (2025 Jun) e202400108, https://doi.org/10.1002/pmic.202400108.
[119] P. Venturini, P.L. Faria, J.V. Cordeiro, AI and omics technologies in biobanking: applications and challenges for public health, Public Health 243 (2025 Jun) 105726, https://doi.org/10.1016/j.puhe.2025.105726.
[120] C.D.M. van Karnebeek, A. O'Donnell-Luria, G. Baynam, A. Baudot, T. Groza, J.J. M. Jans, T. Lassmann, M.C.V. Letinturier, S.B. Montgomery, P.N. Robinson, S. Sansen, R. Mehrian-Shai, C. Steward, K. Kosaki, P. Durao, B. Sadikovic, Leaving no patient behind! Expert recommendation in the use of innovative technologies for diagnosing rare diseases, Orphanet J. Rare Dis. 19 (1) (2024 Sep 27) 357, https://doi.org/10.1186/s13023-024-03361-0.
[121] Z. Obermeyer, B. Powers, C. Vogeli, S. Mullainathan, Dissecting racial bias in an algorithm used to manage the health of populations, Science 366 (6464) (2019 Oct 25) 447–453, https://doi.org/10.1126/science.aax2342.
[122] S. Fatumo, T. Chikowore, A. Choudhury, M. Ayub, A.R. Martin, K. Kuchenbaecker, A roadmap to increase diversity in genomic studies, Nat. Med. 28 (2) (2022 Feb) 243–250, https://doi.org/10.1038/s41591-021-01672-4.
[123] Martin A.R., Kanai M., Kamatani Y., Okada Y., Neale B.M., Daly M.J.. Clinical use of current polygenic risk scores may exacerbate health disparities. Nat Genet. 2019 Apr;51(4):584-591. doi: 10.1038/s41588-019-0379-x. Epub 2019 Mar 29. Erratum in: Nat Genet. 2021 May;53(5):763. doi: 10.1038/s41588-021-00797-z.
[124] Y. Ding, K. Hou, Z. Xu, A. Pimplaskar, E. Petter, K. Boulier, F. Privé, B. J. Vilhjálmsson, L.M. Olde Loohuis, B. Pasaniuc, Polygenic scoring accuracy varies across the genetic ancestry continuum, in: Nature, 618, 2023 Jun, pp. 774–781, https://doi.org/10.1038/s41586-023-06079-4.