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ИММУННЫЕ И МЕТАБОЛИЧЕСКИЕ МЕХАНИЗМЫ РАЗВИТИЯ И СОВРЕМЕННЫЕ ПОДХОДЫ К ТЕРАПИИ СЕРДЕЧНОЙ НЕДОСТАТОЧНОСТИ У ПАЦИЕНТОВ С ВИЧ-ИНФЕКЦИЕЙ

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Immune And Metabolic Mechanisms of Development and Modern Approaches to The Treatment of Heart Failure in Patients with HIV Infection

Резюме

Сердечная недостаточность (СН) остаётся одной из ключевых причин заболеваемости и смертности у пациентов с ВИЧ-инфекцией. За последние десятилетия фенотипы СН у данной популяции претерпели значительные изменения: если ранее доминировала сердечная недостаточность со сниженной фракцией выброса (СНнФВ), то в настоящее время всё большую клиническую значимость приобретает сердечная недостаточность с сохранённой фракцией выброса (СНсФВ). Патогенез этих состояний имеет мультифакторный характер и определяется взаимодействием вирус-ассоциированных механизмов, хронического воспаления, дисрегуляции иммунной системы, кардиометаболических нарушений и побочных эффектов антиретровирусной терапии (АРТ). Для СНнФВ характерны процессы, связанные с хроническим воспалением, активацией моноцитов и макрофагов, ускоренным развитием атеросклероза, ишемической болезни сердца и патологическим ремоделированием миокарда. СНсФВ, напротив, ассоциируется преимущественно с системными метаболическими нарушениями — ожирением, инсулинорезистентностью, дислипидемией, нарушением регуляции кишечного барьера и дисфункцией жировой ткани, что ведёт

к формированию фенотипа кардиометаболической СН. Особую роль в этих процессах играют метаболическое воспаление и специфическое воздействие АРТ (ингибиторов интегразы, нуклеозидных и ненуклеозидных ингибиторов обратной транскрипции). Понимание иммунных и метаболических механизмов ВИЧ-ассоциированной СН открывает перспективы для разработки новых терапевтических подходов, включающих иммуномодуляцию, коррекцию метаболических нарушений, использование статинов, ингибиторов SGLT2 и агонистов GLP-1. Дальнейшие исследования, направленные на стратификацию пациентов и оценку клинических исходов, имеют решающее значение для оптимизации ведения данной сложной категории больных.

Ключевые слова: *сердечная недостаточность; ВИЧ-инфекция; сердечная недостаточность со сниженной фракцией выброса; сердечная недостаточность с сохранённой фракцией выброса; иммунное воспаление; метаболические нарушения; антиретровирусная терапия*

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Abstract

Heart failure (HF) remains one of the leading causes of morbidity and mortality among patients with HIV infection. Over the past decades, the phenotypes of HF in this population have shifted substantially: while heart failure with reduced ejection fraction (HFrEF) was historically predominant, heart failure with preserved ejection fraction (HFpEF) has emerged as an increasingly important clinical manifestation. The pathogenesis of these conditions is multifactorial, driven by virus-related mechanisms, chronic inflammation, immune dysregulation, cardiometabolic disturbances, and adverse effects of antiretroviral therapy (ART). HFrEF in HIV-infected individuals is primarily associated with chronic inflammation, monocyte–macrophage activation, accelerated atherosclerosis, ischemic heart disease, and pathological myocardial remodeling. By contrast, HFpEF is linked to systemic metabolic abnormalities such as obesity, insulin resistance, dyslipidemia, gut barrier dysfunction, and adipose tissue dysregulation, ultimately leading to the cardiometabolic HF phenotype. A central role in this process is played by metabolic inflammation and the impact of ART (including integrase inhibitors, nucleoside and non-nucleoside reverse transcriptase inhibitors). Understanding the immune and metabolic mechanisms of HIV-associated HF opens new opportunities for therapeutic development. Promising approaches include immunomodulation, metabolic correction, and the use of statins, SGLT2 inhibitors, and GLP-1 receptor agonists. Future studies focusing on patient stratification and clinical outcomes are essential for optimizing the management of this complex patient group.

Key words: *heart failure, HIV infection, heart failure with reduced ejection fraction, heart failure with preserved ejection fraction, immune inflammation, metabolic disorders, antiretroviral therapy*

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ART — antiretroviral therapy, HIV — human immunodeficiency virus, BMI — body mass index, IL — interleukin, LV — left ventricle, HDLP — high-density lipoproteins, LDLP — low-density lipoproteins, MRI — magnetic resonance imaging, RR — relative risk, HF — heart failure, HFrEF — heart failure with reduced ejection fraction, HFpEF — heart failure with preserved ejection fraction, CRP — C-reactive protein, FMT — faecal microbiota transplantation, EF — ejection fraction, ECG — electrocardiography, AIDS — acquired immune deficiency syndrome, IL-1β — interleukin-1β, IL-6 — interleukin-6, NLRP3 — NOD-like receptor protein 3, TLR — Toll-like receptor, SGLT2 — sodium-glucose linked transporter 2, GLP-1 — glucagon-like peptide-1, INSTI — integrase inhibitors, NRTI — nucleoside reverse transcriptase inhibitors, NNRTI — non-nucleoside reverse transcriptase inhibitors, TMAO — trimethylamine N-oxide, MACE — major adverse cardiovascular events

Introduction

Heart failure (HF) has been regarded for several decades as one of the most unfavourable clinical outcomes in patients living with HIV infection; however, its characteristics have changed substantially over the past forty years [1]. Before the advent of antiretroviral therapy (ART), HF in HIV-infected patients was predominantly associated with complications of acquired immunodeficiency syndrome (AIDS), including severe uncontrolled viremia, opportunistic infections, and the related dilated cardiomyopathies [2].

With the introduction and widespread use of ART, the life expectancy of patients with HIV has increased significantly, leading to a shift in the pattern of morbidity,

with cardiovascular diseases emerging as a major concern in this population [3, 4]. Despite the overall progress in reducing mortality achieved through ART, HIV-positive patients continue to have a significantly higher risk of developing HF compared with the general population [5, 6].

It should be emphasised that, in contemporary clinical practice, HF and associated cardiovascular diseases in patients with HIV are only partially explained by traditional risk factors observed in the general population. Mechanisms specific to chronic HIV infection continue to play a substantial role, including persistent systemic inflammation, immune dysregulation, and the consequences of prolonged viral persistence, all of which contribute to both the development and progression of HF [7].

The clinical spectrum of HF in this patient population is heterogeneous and is determined by the interplay of multiple etiological factors. The most widely used approach to classifying HF remains stratification according to left ventricular ejection fraction (LVEF). This classification distinguishes heart failure with reduced ejection fraction (HFrEF), which is predominantly associated with systolic dysfunction, from heart failure with preserved ejection fraction (HFpEF), which is characterised by diastolic dysfunction and a high prevalence of systemic comorbid conditions in the absence of a marked reduction in LVEF [8].

Importantly, therapeutic strategies for HFrEF and HFpEF differ and require the implementation of distinct management algorithms [8]. In recent years, there has been growing recognition that these phenotypes represent heterogeneous clinical pathophysiological subpopulations characterised by unique mechanisms underlying disease development and progression. This has opened new avenues for the development of individualised therapeutic approaches.

People living with HIV exhibit an increased risk of both HF overall and the development of the HF phenotype with HFpEF. In this context, understanding the precise pathophysiological mechanisms underlying the various forms of HF in this population is of fundamental importance for optimising therapeutic strategies and selecting individualised approaches [9–11]. This review examines the key mechanisms through which HIV infection may exert both direct and indirect effects on the development of different HF subtypes and clinical manifestations, including HFrEF and HFpEF.

The purpose of this review is to systematise and critically analyse the present knowledge of the immune and metabolic mechanisms of heart failure in patients with HIV infection; and to evaluate the impact of antiretroviral therapy and the possibility of using novel therapeutic strategies to correct these conditions.

Methods of study search

A literature search was conducted in PubMed/MEDLINE, Scopus, Web of Science and eLibrary for the period from January 2000 to March 2024. The following keywords and keyword combinations were used for the search: “HIV infection”, “heart failure”, “HFrEF”, “HFpEF”, “immune mechanisms”, “immune dysregulation”, “metabolic disorders”, “metabolic inflammation”, “antiretroviral therapy”. At the first stage, all publications containing the specified keywords in the title or abstract were considered. At the second stage, sources were filtered by publication type; the analysis included original studies, systematic reviews, meta-analyses, clinical practice guidelines, and expert statements issued by relevant professional associations. At the third stage, articles without full-text access, duplicate publications, and studies in which heart failure in HIV-infected individuals was addressed only indirectly were excluded. The final set of publications was established following an independent assessment of relevance by two authors. As a result of the selection process, 67 publications that most comprehensively reflect the current state of knowledge on the subject were included in this review.

Epidemiology of HIV and heart failure

Over the past decades, a substantial body of evidence has accumulated demonstrating an increased incidence and prevalence of HF among people living with HIV infection compared with the general population [9]. The risk of HF in HIV-infected patients is 1.5-2 times higher than in non-infected population [12]. A large cohort study of veteran ageing, which included the US national data for 2003–2016, demonstrated that in HIV patients the risk of HF was significantly higher than in individuals living without HIV (RR 1,6), despite regular ART [9].

Similar results were reported in a national study based on the Taiwanese databases, where it was demonstrated that ART reduces the risk of HF; however, even in patients undergoing treatment, the probability of HF remains 1.5 times higher than in non-HIV patients [10]. In a single-centre study conducted within an urban healthcare system between 2000 and 2016, the risk of HF among people living with HIV and pulmonary hypertension was found to be more than twice as high as that among patients without HIV infection [6].

It is important to emphasise that many early studies demonstrating an increased risk of HF among people living with HIV included cohorts in which access to ART was limited. Nevertheless, even in contemporary studies focusing exclusively on patients receiving ART, the prevalence of HF remains high. For example, one recent multicentre study reported a prevalence of HFrEF of 2.4 % [13]. Furthermore, individuals with HIV continue to have an intrinsically elevated risk of developing HF compared not

only with the general population but also with patients affected by other chronic inflammatory diseases [14].

Recent observations demonstrate that the HFpEF phenotype prevails in the structure of HF in HIV-positive patients. For instance, HEART with HIV study showed that in individuals living with HIV, the risk of both HFrEF and HFpEF is higher than in people without HIV, and the relative risk of HFpEF turns out to be more pronounced [5]. Imaging studies have shown that the prevalence of diastolic dysfunction among middle-aged patients may range from 22 % to 37 % [11, 13, 17–19].

Data from a meta-analysis of 54 studies encompassing North America, Europe, Africa, and Asia further underscore the global nature of this problem: the prevalence of left ventricular systolic dysfunction was 12.3 %, whereas the prevalence of diastolic dysfunction reached 29.3 % [11]. Although the exact relationship between subclinical abnormalities and the development of clinically overt HF remains incompletely understood, the observed differences in the prevalence of diastolic and systolic dysfunction suggest a potential shift in the disease spectrum toward a higher prevalence of HFpEF among HIV-infected patients [15, 16]. This emphasises the need in further prospective studies in order to clarify pathogenetic mechanisms and predict long-term outcomes.

Clinical presentation of heart failure in patients living with HIV infection depends to a greater extent on the stage of the infectious process. During the acute phase of HIV infection, cases of heart failure are observed predominantly in the setting of myocarditis and transient myocardial dysfunction associated with high viral load and marked immune activation. During the chronic (latent) stage, persistent systemic inflammation, immune dysregulation, and metabolic disturbances become the predominant factors, creating the conditions for the development of heart failure with preserved ejection fraction. In contrast, during disease progression and the development of AIDS, severe forms of heart failure with reduced ejection fraction are more commonly encountered, resulting from direct cardiomyocyte injury, opportunistic infections, and dilated cardiomyopathy. Thus, the clinical course of HF in HIV infection reflects both the stage of the infectious process and the interplay among virus-related, immune-mediated, and metabolic mechanisms.

Heart failure with reduced ejection fraction in HIV: phenotypes and pathogenetic mechanisms

Traditionally, heart failure with reduced ejection fraction in HIV-infected population is associated with cardiomyocyte death, structural remodelling, and formation of fibrosis resulting in reduced systolic function of the left ventricle [20]. During the early years of the HIV/AIDS epidemic, HF frequently developed as a consequence of direct myocardial injury, including infection of cardiomyocytes and immune cells by the virus, the toxic effects of HIV proteins, and opportunistic infections, all of which contributed to the development of dilated cardiomyopathy [21]. Although such an etiology has become less common in the era of highly effective ART, it remains relevant among populations with limited access to treatment [11].

Modern mechanisms of CFrEF

At present, chronic inflammation and immune dysregulation, which persist even in the setting of successful ART, play a central role [22]. In most patients, residual viremia persists, promoting sustained activation of innate immune cells, particularly monocytes and macrophages [23]. Specifically, the proportion of non-classical proinflammatory monocytes (CD16+) in individuals with HIV may account for up to 40 % of circulating mononuclear cells, compared with 5–10 % in HIV-negative individuals [24]. These cells produce cytokines and chemokines that maintain a chronic inflammatory state within the myocardium [25].

Dysregulated monocyte-macrophage activation contributes to the accelerated development of atherosclerosis, coronary artery disease, and myocardial infarction in patients with HIV infection. These effects are mediated through enhanced production of reactive oxygen species, increased expression of adhesion molecules and chemokines, foam cell formation, and accelerated progression of atherosclerotic plaques [26]. Subsequent myocardial infarctions, accompanied by replacement of damaged myocardium with scar tissue, lead to ischemic cardiomyopathy and HFrEF [27, 28].

Role of epidemiological factors

In addition to biological mechanisms, social and behavioural factors have substantial significance. Smoking is substantially more prevalent among patients with HIV infection than in the general population [29], thereby contributing to the development of atherosclerosis and HFrEF. Similarly, the higher prevalence of methamphetamine use among people living with HIV [30] has been associated with an increased risk of toxic cardiomyopathies and HFrEF [31]. Although the available data regarding this association are inconsistent, further studies are needed to clarify its role in the spectrum of HF among patients with HIV [32].

Cardiac fibrosis and chronic inflammation

Profibrotic effect of chronic inflammation is of particular significance. HIV-infected monocytes and macrophages produce excessive IL-1β, which activate inflammasome NLRP3 and resident immunocytes in the heart, causing enhanced myocyte apoptosis, collagen synthesis, and scarring [33,34]. In addition, HIV proteins activate

TLR-receptors, thereby amplifying inflammatory signalling cascades [35]. Dysfunction of regulatory T cells promotes the overproduction of transforming growth factor-β1 (TGF-β1) and the activation of myofibroblasts [36].

Impaired intestinal barrier as a factor of HFrEF

Acute HIV-infection is associated with destruction of CD4+ T cells in the intestine and epithelial integrity damage, resulting in translocated microbial products and activation of TLR/NLRP3-inflammasome [37]. In addition, HIV-infected individuals exhibit enhanced production of intestinal metabolites, including trimethylamine N-oxide (TMAO), which is associated with development of cardiac fibrosis [38]. These alterations persist even with successful ART, thereby maintaining a sustained risk of HFrEF progression [39].

Thus, HFrEF in people living with HIV results from a combination of conventional factors, such as coronary artery disease and toxic insults, and mechanisms unique to this population, including chronic inflammation, profibrotic signalling pathways, and disruption of the intestinal barrier. Even in the era of highly effective ART, these processes continue to drive myocardial remodelling and the progression of heart failure.

Therapeutic approaches to heart failure with reduced ejection fraction in HIV-infected patients

Core principles

Regardless of HIV status, the cornerstone of treatment for HFrEF remains guideline-directed medical therapy, including β-blockers, inhibitors of the renin-angiotensin-aldosterone system, mineralocorticoid receptor antagonists, and SGLT2 inhibitors; treatment selection and dose titration are performed according to the general management algorithms for HFrEF [8]. Against this background, additional strategies (primarily anti-inflammatory and immunomodulatory approaches) are being explored in HIV-infected individuals as potential adjunctive therapies for patients with a persistent inflammatory phenotype of myocardial remodelling.

IL-1β inhibition

In pilot studies involving HIV-infected individuals, canakinumab, a monoclonal antibody targeting IL-1β, has been shown to reduce systemic inflammation and signs of atherosclerotic disease, making the IL-1β-inflammasome axis an attractive therapeutic target in the subgroup of patients with residual inflammatory activity despite virologic suppression [40]. However, evidence regarding their impact on major cardiovascular outcomes in HIV-infected patients with HFrEF remains insufficient.

IL-6 blockage and inflammasome targeting

Approaches aimed at suppressing the cytokine cascade are currently being investigated, including the use of tocilizumab, an IL-6 receptor inhibitor, as well as direct targeting of the NLRP3 inflammasome with experimental antagonists of its subunits [40]. These strategies are pathophysiologically justified, given the role of IL-6-mediated myeloid cell activation and the central involvement of NLRP3 in fibrogenesis. However, they require rigorous evaluation of their safety profile in patients with HIV infection, particularly with regard to the risk of opportunistic infections and potential drug interactions with ART.

TLR signalling modulation

In order to inhibit the innate immune activation, the use of 4-aminoquinoline (hydroxychloroquine) for regulation of TLR-mediated signalling has been studied [41]. Correct positioning of such devices is possible only within the scope of clinical studies among thoroughly selected patients having the signs of the inflammatory phenotype of remodelling.

Intestinal barrier and microbiota

Given the contribution of HIV-associated intestinal barrier dysfunction to the maintenance of systemic inflammation and profibrotic signalling pathways, including TLR- and NLRP3-mediated activation, interventions aimed at restoring enterocyte integrity and the composition of the gut microbiota are currently being investigated. These include probiotics and faecal microbiota transplantation (FMT) [41, 42]. Although the pathogenetic rationale for these approaches is compelling, randomised trials with clinically relevant endpoints in patients with HFrEF are still required.

Clinical significance and patient selection criteria

At the present stage, immunomodulatory therapy in HIV-infected patients with HFrEF should be regarded solely as an adjunct to guideline-directed medical therapy and optimised ART, and should be implemented exclusively within the framework of clinical protocols. Such approaches should incorporate targeted stratification based on biomarkers of residual inflammation (e.g., high-sensitivity C-reactive protein, IL-6, sCD14, and sCD163), evidence of myocardial fibrosis (as assessed by cardiac MRI with T1/ECV mapping), and the presence of stable virologic suppression. Key endpoints should include reverse left ventricular remodelling, heart failure-related hospitalisations, and composite major adverse cardiovascular events (MACEs). Careful assessment of safety and potential interactions with ART is mandatory, particularly with respect to CYP-mediated mechanisms and effects involving P-gp substrates.

Limitations and safety

The majority of the above-mentioned approaches (IL-1β/IL-6 inhibitors, anti-NLRP3, FMT) does not have a confirmed advantage in clinical outcomes in HIV-infected patients with HFrEF and has not been included in the standards of care. Risks of immune suppression, latent infection reactivation and the impact on the vaccine-mediated response require thorough evaluation within the scope of clinical trials [40–42].

Heart failure with preserved ejection fraction in HIV-infected individuals

Whereas HFrEF was the predominant HF phenotype during the early years of the HIV epidemic, contemporary trends indicate an increasing prevalence of HFpEF [8]. In contrast to HFrEF, which is characterised by cardiomyocyte loss and replacement fibrosis, HFpEF is driven predominantly by systemic comorbidities and cardiomyocyte dysfunction in the absence of substantial cytolytic cell death [15, 43]. Traditionally, HFpEF has been regarded as a consequence of hypertensive heart disease, occurring mainly in elderly patients in whom increased myocardial stiffness limits diastolic relaxation [44].

In HIV-infected individuals, chronic activation of innate immune cells (monocytes and macrophages) is associated with systemic inflammation, stiff aorta and increased vascular rigidity, which is pathophysiologically similar to the mechanisms of hypertensive disease [45]. The mechanisms of pathological fibrosis formation, which were previously discussed for HFrEF, can manifest as the HFpEF phenotype even before systolic dysfunction develops [46]. Numerous studies in patients with HIV have demonstrated increased activity of the monocyte-macrophage compartment, including peripheral monocytosis and enhanced production of chemokines and cytokines involved in chemotaxis and the maintenance of chronic inflammation [47]. Taken together, these factors create a milieu that predisposes HIV-infected individuals to an increased susceptibility to the development of HFpEF.

Cardiometabolic dysfunction and metabolic inflammation

Although arterial hypertension remains one of the most important risk factors of HFpEF, the data for the last 15 years demonstrate that cardiometabolic dysfunction plays an equally important role [48]. Obesity and metabolic syndrome are associated with increased secretion of inflammatory cytokines, including IL-6, which promotes the so-called metabolic inflammation. This process both initiates and worsens HFpEF [49].

Experimental models have demonstrated that systemic inflammation induces tissue hypoxia, which metabolically reprograms both innate and adaptive immune cells, shifting their energy metabolism from mitochondrial respiration to anaerobic glycolysis [50]. This state of energetic stress disrupts the transcription of regulatory genes, promotes dysfunction of resident myocardial immune cells, diminishes their cardioprotective capacity, and impairs the processes responsible for the resolution of inflammation [51]. As a consequence, chronic diastolic dysfunction develops in the absence of overt cardiomyocyte death [52]. With the increasing prevalence of obesity, this cardiometabolic phenotype of HFpEF is becoming increasingly important, including among younger patients [43].

The role of retroviral therapy

A significant risk factor of metabolic disorders in HIV patients is the side effects of ART. Early regimens that included protease inhibitors were associated with pronounced disturbances in lipid metabolism, lipodystrophy, and obesity [53]. Although these agents have largely been replaced, even contemporary ART regimens, including integrase strand transfer inhibitors (INSTIs), nucleoside reverse transcriptase inhibitors (NRTIs), and non-nucleoside reverse transcriptase inhibitors (NNRTIs), have been associated with weight gain and alterations in body fat distribution [54, 55].

Recent pre-clinical studies demonstrated that the widely used first-line agents, such as Dolutegravir and Bictegravir, stimulate adipogenesis, adipocyte hypertrophy and facilitate obesity [56]. Moreover, INSTIs may disrupt the physiological processes of adipose tissue accumulation, thereby inducing adipocyte hypoxia, oxidative stress, and insulin resistance [57]. Thus, despite the undeniable benefits of ART in reducing mortality, its metabolic adverse effects contribute additionally to the increasing prevalence of HFpEF among patients living with HIV.

Dysregulation of intestinal barrier and adipose tissue

An important component of pathogenesis is disrupted intestinal barrier in HIV infection. Loss of enterocyte layer integrity and the translocation of lipopolysaccharides into the bloodstream lead to activation of inflammatory cascades, reduced efficiency of reverse cholesterol transport, and impaired HDLP function [58]. These processes exacerbate dyslipidemia and metabolic stress, thereby increasing the risk of atherosclerosis and metabolic inflammation.

In addition, some HIV-associated proteins have been shown to inhibit preadipocyte differentiation even in the presence of low-level viremia. This results in adipocyte hypertrophy, hyperglycemia, and organ steatosis, even in individuals with a normal body mass index [59]. HIV infection is also associated with impaired function of dicer-RNAse and white fat dysfunction [60]. In the adipose tissue of HIV-infected individuals, increased infiltration by CD8+ T cells has been observed even in those with

a normal BMI, resembling the pattern seen in obese individuals without HIV infection [59, 61]. Such infiltration amplifies adipocyte inflammation and promotes the development of insulin resistance and metabolic syndrome.

HFpEF in HIV-infected individuals represents a multifactorial phenotype driven by the interplay among chronic inflammation, metabolic disturbances, adverse effects of ART, and dysfunction of the intestinal barrier and adipose tissue. These processes confer an increased predisposition to the cardiometabolic form of HF, even in patients without traditional risk factors such as obesity and hypertension. Consequently, HFpEF is emerging as the predominant clinical phenotype of heart failure in the population of patients living with HIV infection.

Therapeutic approaches to heart failure with preserved ejection fraction in HIV-infected patients

Given the increasing prevalence of cardiometabolic heart failure in both the general population and among people living with HIV, as well as the particular susceptibility of this patient group to cardiometabolic disturbances, optimisation of therapeutic strategies aimed at reducing metabolic inflammation has become of paramount importance. These strategies encompass both non-pharmacological approaches, such as lifestyle modification, and pharmacological interventions.

Statins and dyslipidemia

One of the most extensively studied strategies is the use of statins for the management of dyslipidemia. Their efficacy in lowering cholesterol levels and preventing cardiovascular complications has long been established in the general population. The latest European guidelines on the management of dyslipidemias recommend statin therapy for individuals aged 40 years and older living with HIV for primary prevention, regardless of estimated cardiovascular risk or LDLP levels, in order to reduce the risk of cardiovascular events; the choice of statin should be guided by the potential for drug-drug interactions [62]. Available evidence indicates that statins also possess substantial preventive potential with respect to cardiovascular events in people living with HIV [41, 43, 63]. Of particular importance are the findings of the large REPRIEVE trial, in which pitavastatin significantly reduced the 5-year risk of major adverse cardiovascular events in patients with HIV infection, underscoring the role of this strategy in the prevention of cardiometabolic heart failure [64].

SGLT2 inhibitors

Beyond lipid-lowering therapy, there is growing interest in conventional heart failure treatments that exert anti-inflammatory and metabolically modulating effects. In the EMPEROR-Preserved trial, treatment with empagliflozin was associated with a reduction in heart failure-related hospitalisations among patients with HFpEF. Additional biomarker analyses suggest that the cardioprotective effects of this SGLT2 inhibitor may be mediated, at least in part, by improvements in mitochondrial function and reductions in oxidative stress [65, 66].

GLP-1 receptor agonists

Another promising strategy is the use of GLP-1 receptor agonists. In the STEP-HFpEF trial, treatment with semaglutide in patients with obesity resulted in significant improvements in HF symptoms and functional status, as well as a 43.5 % reduction in C-reactive protein levels [67]. Moreover, data from a phase IIb clinical trial involving HIV-infected individuals receiving ART demonstrated that semaglutide promotes weight loss, reduces waist circumference, and improves markers of metabolic dysfunction-associated liver disease associated with an inflammatory phenotype [68].

The role of metabolic inflammation as a therapeutic target

Taken together, these findings suggest that metabolic inflammation may represent a viable therapeutic target in cardiometabolic HFpEF among patients living with HIV infection. However, further studies are needed to determine the optimal combinations of anti-inflammatory and metabolic therapies and to assess the extent to which modulation of metabolic inflammation can improve long-term outcomes in HFpEF.

Conclusion

The evidence discussed above highlights the numerous and diverse mechanisms through which HIV infection contributes to the development of both HFrEF and HFpEF. Regardless of the clinical phenotype, whether characterised by enhanced myocardial fibrosis, increased susceptibility to atherosclerotic disease, disruption of myocardial immune cell organisation, or alterations in cardiomyocyte metabolism, the central pathophysiological theme remains dysregulation of the innate and adaptive immune systems, resulting in chronic pathological inflammation.

In recent years, the concept of metabolic inflammation as a driving force underlying the cardiometabolic phenotype of HF has attracted particular interest. This concept opens new therapeutic opportunities, including strategies aimed at immunomodulation and the correction of metabolic disturbances.

Given that the prevalence of cardiometabolic HF is increasing both in the general population and among people living with HIV, future research should focus on elucidating the interplay among immune dysregulation, chronic inflammation, and altered metabolism. A deeper understanding of these interactions is crucial for the development of targeted therapeutic strategies capable of improving outcomes in patients with HIV infection.

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