Research progress on the comorbidity of heart failure and type 2 diabetes mellitus in the elderly: a preprint

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Abstract

Heart failure and type 2 diabetes frequently coexist in the elderly population, with a bidirectional vicious cycle in their pathophysiological mechanisms involving insulin resistance, chronic inflammation, neuroendocrine activation, and inter-organ crosstalk, all of which are exacerbated by aging. Their clinical manifestations are insidious and highly heterogeneous, and diagnosis requires precise assessment integrating imaging and biomarkers. In terms of treatment, the principle of "co-management of comorbidities" should be followed, using novel anti-heart failure agents—represented by sodium-glucose cotransporter 2 inhibitors and angiotensin receptor–neprilysin inhibitors—as therapeutic cornerstones, and prioritizing glucose-lowering agents that provide both cardiac and renal benefits. Establishing a comprehensive, multidisciplinary team–based management model is key to improving prognosis. Future work needs to include dedicated studies on comorbidities in the elderly and to explore new directions such as cell therapy, anti-aging targeted interventions, and digital health. This review aims to systematically summarize the disease burden, pathophysiological mechanisms, clinical features, therapeutic strategies, and future directions of cardio-diabetic comorbidity in older adults, thereby providing a reference for optimizing its clinical management.

Full Text

Comorbidity of Diabetes and Heart Failure in the Elderly Population: A Systematic Review

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Abstract

Heart failure (HF) and type 2 diabetes mellitus (T2DM) frequently coexist in the elderly population, characterized by a bidirectional pathophysiological mechanism involving insulin resistance, chronic inflammation, neuroendocrine activation, and inter-organ crosstalk, which is further exacerbated by the aging process. Clinical manifestations are often insidious and highly heterogeneous, requiring precise assessment through a combination of imaging modalities and biomarkers. Treatment should adhere to the principle of "co-morbidity co-treatment," with novel HF therapeutics such as sodium-glucose cotransporter 2 inhibitors (SGLT2i) and angiotensin receptor-neprilysin inhibitors (ARNI) serving as cornerstone therapies, while prioritizing glucose-lowering agents with concurrent cardiorenal benefits. Establishing a comprehensive management model through multidisciplinary teams is key to improving prognosis. Future research should focus on conducting specialized studies targeting elderly patients with comorbidities and exploring emerging directions such as cell therapy, aging-targeted interventions, and digital health. This review aims to systematically summarize the disease burden, pathogenic mechanisms, clinical characteristics, treatment strategies, and future directions of comorbid diabetes and HF in the elderly, providing a reference for optimizing clinical management of this patient population.

Keywords: Heart failure; Diabetes mellitus, type 2; Aged; Multiple chronic conditions; Multidisciplinary management; Review

1. Literature Search Strategy

This study is a narrative review aimed at systematically summarizing and synthesizing existing evidence. To ensure comprehensive coverage of relevant literature, we conducted computerized searches of PubMed, China National Knowl-

edge Infrastructure (CNKI), and Wanfang Data Knowledge Service Platform, with the search period set from January 2020 to August 2025 (with the exception of some classic studies and mechanism-related papers). Chinese search terms included "heart failure," "type 2 diabetes," "comorbidity," "elderly patients," "mechanism," "therapy," and "comprehensive management," while English search terms included "Heart failure," "Type 2 diabetes," "Comorbidity," "Older patients," "Mechanism," "Therapy," and "Comprehensive Management." Initial screening was performed by reviewing titles and abstracts, followed by full-text review to determine final eligibility. Inclusion criteria comprised studies focusing on the comorbidity of HF and T2DM, covering pathophysiological mechanisms, clinical characteristics, treatment strategies, and management, with particular emphasis on literature involving elderly subgroups or studies specifically targeting older adults. Exclusion criteria comprised unrelated studies, unpublished work, and articles where the full text was unavailable. A total of 73 articles were ultimately included.

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2. Pathophysiological Mechanisms of Comorbid HF and T2DM in the Elderly

The comorbid state of HF and T2DM arises from a complex pathophysiological network woven together by multiple dimensions including insulin resistance, chronic inflammation, and neuroendocrine activation. Aging, as an independent risk factor, exacerbates damage at each of these pathways, rendering elderly patients' hearts more vulnerable to injury with diminished repair capacity and resulting in more severe clinical outcomes. HF and T2DM share a close and complex bidirectional relationship: T2DM is an independent risk factor for the development and progression of HF, while HF status can also exacerbate insulin resistance through mechanisms such as neuroendocrine activation, thereby increasing the risk of new-onset T2DM. This vicious cycle is amplified in elderly individuals due to age-related physiological decline, multimorbidity, and inflammatory aging, leading to more insidious clinical manifestations, greater treatment complexity, poorer prognosis, and significantly higher rates of rehospitalization and mortality.

2.1 Insulin Resistance and Metabolic Dysregulation Insulin resistance represents the core link connecting HF and T2DM. Under this condition, cardiomyocyte energy metabolism shifts from efficient glucose oxidation to inefficient fatty acid oxidation, resulting in insufficient ATP production, accumulation of toxic lipid intermediates, and induction of lipotoxicity, which directly impairs cardiomyocyte function and promotes interstitial fibrosis—representing one of the important initiating mechanisms of HF with preserved ejection fraction (HFpEF). The severity of insulin resistance carries clear prognostic value; the triglyceride-glucose index (TyG index), which reflects insulin resistance, is not only independently associated with HF deterioration and mortality risk, but

its dynamic trajectory is even more meaningful: a high baseline TyG index with a significant declining trend is independently associated with increased risk of long-term HF worsening and overall mortality. This suggests that insulin resistance is a dynamic indicator throughout the entire course of comorbidity rather than a static baseline risk factor. Elderly individuals inherently exhibit age-related declines in insulin sensitivity and mitochondrial function, which depletes cardiac compensatory reserve and renders the aging heart more susceptible to rapid decompensation and progression to severe myocardial dysfunction when confronted with T2DM-related metabolic stress.

2.2 Chronic Inflammation and Oxidative Stress Chronic low-grade inflammation represents a shared mechanism in the progression of both HF and T2DM. Hyperglycemia and insulin resistance can activate key inflammatory pathways including the NOD-like receptor thermal protein domain associated protein 3 (NLRP3) and nuclear factor-κB (NF-κB), promoting the release of pro-inflammatory cytokines such as tumor necrosis factor-α and interleukin-6, which directly drive cardiomyocyte apoptosis, hypertrophy, and interstitial fibrosis. Large-scale clinical analyses have confirmed that systemic inflammation is present in approximately half of HF patients, independent of left ventricular ejection fraction (LVEF) but significantly correlated with the number of comorbidities including obesity, diabetes, and chronic kidney disease (CKD). This indicates that inflammation serves as a central hub connecting and amplifying the "cardio-metabolic" comorbidity network rather than being a secondary manifestation of HF. When such pathological inflammation is superimposed on the elevated baseline inflammatory levels characteristic of physiological aging, the myocardial damage effect is exponentially amplified, greatly promoting cardiac remodeling and functional deterioration.

2.3 Neuroendocrine Activation and Cardiac Remodeling Overactivation of the sympathetic nervous system (SNS) and renin-angiotensin-aldosterone system (RAAS) represents a core driver of HF progression. In comorbid T2DM, hyperglycemia and autonomic neuropathy can further exacerbate SNS activation, while overactivated RAAS not only promotes cardiac fibrosis and remodeling but also directly aggravates insulin resistance and pancreatic β-cell dysfunction, forming another "cardio-metabolic" vicious cycle. Elderly individuals exhibit diminished regulatory capacity of neuroendocrine systems and poorer tolerance to neuroendocrine activation, making the destructive potential of this vicious cycle even more pronounced. This poses more complex demands on the responsiveness and tolerability to conventional pharmacological therapies (such as β-blockers and RAAS inhibitors) in clinical practice.

2.4 Diabetic Cardiomyopathy (DCM) DCM represents the culmination of the aforementioned pathological mechanisms. Myocardial fibrosis is a characteristic early pathological change, while accumulation of advanced glycation end products (AGEs) exacerbates oxidative stress and inflammation and cross-

links with myocardial collagen, directly reducing myocardial compliance. This process involves abnormal activation of multiple signaling pathways including peroxisome proliferator-activated receptors, mitogen-activated protein kinases, and protein kinase C, with novel therapeutic agents targeting these pathways (such as pemafibrate and berberine) currently under investigation. Furthermore, novel biomarkers including receptor tyrosine kinases (downregulated) and heat shock proteins (upregulated) have been identified as independently associated with ventricular dysfunction and HF risk in diabetic patients, revealing new molecular pathways mediating diabetic myocardial injury. These biomarker alterations are detectable in circulating blood and hold promise as novel indicators for cardiac risk assessment.

The European Society of Cardiology defines DCM as cardiac structural and functional abnormalities caused by diabetes in the absence of coronary artery disease, hypertension, or valvular disease. However, current consensus considers this "purified" concept to have limited clinical utility because diabetes rarely acts in isolation. The prevailing clinical perspective tends to view DCM as a contributing factor throughout the entire course of HF development, typically coexisting with obesity and hypertension to cause cumulative myocardial damage. Therefore, elderly T2DM patients with subclinical cardiac abnormalities should be considered as being in the "pre-HF" stage—a critical window period where aggressive intervention may delay HF onset and progression.

Recent research is driving a paradigm shift in comorbidity pathological patterns, moving from isolated diseases toward consideration of multi-system integrated effects. In this model, the liver-heart axis (sharing lipotoxicity and fibrosis pathways), gut-heart axis (mediated by microbial metabolites), adipose-cardiac axis (visceral fat driving inflammation and fibrosis through adipokine dysregulation), and immunometabolism collectively form a complex "inter-organ crosstalk" network that intimately links metabolic reprogramming, chronic inflammation and immune dysregulation, endothelial dysfunction, and myocardial fibrosis. In elderly patients already experiencing multi-system functional decline, this inter-organ vicious cycle is particularly prominent. Consequently, in-depth understanding and effective intervention for HF and T2DM comorbidity must be grounded in breaking this inter-organ vicious cycle rather than merely targeting single organs or pathways.

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3. Clinical Heterogeneity and Diagnostic Challenges in Elderly Patients with Comorbid HF and T2DM

3.1 Insidious and Atypical Clinical Manifestations Elderly HF patients with comorbid T2DM often exhibit worse cardiac function yet more insidious symptoms. A propensity score-matched study of elderly HF patients found that those with T2DM had significantly lower peak oxygen uptake (peak VO_2) and heart rate reserve during exercise testing compared to controls (15.7 vs. 17.3,

P<0.01). Peripheral vascular disease limits patients' exercise tolerance, while autonomic nerve injury blunts perception of chest tightness and fatigue, often resulting in HF being undetected until obvious lower extremity edema or nocturnal paroxysmal dyspnea develops. Additionally, elderly patients may have other chronic diseases, leading to more complex and diverse symptom presentations. For example, lower extremity edema may result from both HF fluid retention and hypoalbuminemia due to diabetic nephropathy, while dyspnea may stem from either HF-induced pulmonary congestion or respiratory regulation disorders such as obesity hypoventilation syndrome.

3.2 Heterogeneity of HF Phenotypes T2DM can lead to multiple HF phenotypes including HF with reduced ejection fraction (HFrEF) and HFpEF, with HFpEF being more common and related to the pathophysiology of diabetic cardiomyopathy. A cluster analysis of over 2,300 elderly HFpEF patients with 18 comorbidities identified four phenotypes, one of which was "CKD-anemia-T2DM."Machine learning-based "phenotype mapping"studies have also identified HFpEF subtypes dominated by diabetes. In contrast, HFrEF patients are more likely to have coexisting coronary artery disease and hypertension in addition to T2DM. Therefore, when elderly T2DM patients develop HF symptoms, both HF subtypes should be considered: ischemic cardiomyopathy leading to HFrEF, and non-ischemic factors leading to HFpEF, which require differentiation based on medical history and examination findings.

3.3 Integrated Application of Diagnostic Tools and Biomarkers Echocardiography is the cornerstone for diagnosis and phenotyping, effectively detecting asymptomatic left ventricular diastolic dysfunction (which can occur in up to 70% of elderly T2DM populations) and enabling initial classification through LVEF measurement. Beyond traditional echocardiographic parameters, global longitudinal strain (GLS) obtained through emerging cardiac magnetic resonance feature tracking technology is an independent predictor of adverse cardiovascular events in HFpEF patients with T2DM. Its sensitivity for detecting subclinical myocardial dysfunction surpasses that of LVEF and is not confounded by common comorbidities, making it a robust and promising indicator for precise risk stratification. Concurrently, screening for myocardial injury markers and electrocardiograms should be emphasized. Natriuretic peptides have clear value in differentiating causes of dyspnea and assessing prognosis, though their levels may be influenced by age-related renal insufficiency and obesity, requiring comprehensive clinical interpretation. Routine troponin testing during acute decompensated HF helps exclude occult myocardial infarction, which is common in elderly patients. Furthermore, novel biomarkers targeting inflammatory pathways, such as receptor tyrosine kinases (downregulated) and heat shock proteins (upregulated) detectable in circulation, hold promise as new diagnostic indicators.

Given the close bidirectional relationship between HF and diabetes, systematic assessment of glycemic status (including HbA1c and oral glucose tolerance tests

in high-risk populations) should become standard practice for all newly diagnosed or follow-up HF patients. International authoritative guidelines such as those from the American Diabetes Association have begun recommending HF screening in asymptomatic diabetic patients. However, current evidence-based medicine (such as the positive predictive value of N-terminal pro-B-type natriuretic peptide in asymptomatic populations and intervention benefits) does not appear to support these recommendations. The large number of false-positive results from low positive predictive values would subject healthy populations to unnecessary further examinations and medical expenses. Considering the characteristics of China' s healthcare system, a more cost-effective and pragmatic approach of precise screening and tiered management is recommended: prioritizing screening resources for high-risk elderly T2DM patients with advanced age and multiple comorbidities, using NT-proBNP for initial screening, and referring positive cases to cardiology or chronic disease management teams for integrated management. This approach aligns with the tiered healthcare system, achieving shifting management upstream and enabling effective intervention in the early stages of HF progression.

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4. Treatment Strategies and Comprehensive Management of Comorbid HF and T2DM in the Elderly

Treatment of elderly patients with comorbid HF and T2DM aims to alleviate HF symptoms, reduce rehospitalization and mortality rates, and improve prognosis. When formulating treatment plans, the interplay between the two diseases, age-related physiological changes, multimorbidity, and complexities of polypharmacy must be considered holistically to construct a patient-centered, individualized, multidisciplinary management model.

4.1 Synergistic Effects of Novel Cornerstone Medications SGLT2 inhibitors have transitioned from glucose-lowering agents to first-line core therapeutics across the entire HF spectrum. Multiple large-scale trials (DAPA-HF, EMPEROR-Reduced, EMPA-REG Outcome, etc.) have demonstrated that SGLT2i consistently reduce cardiovascular death or HF hospitalization and provide significant renal protection regardless of T2DM status. Their clinical benefits have been confirmed in both HFrEF and HFpEF, with the 2023 ESC Heart Failure Guidelines and 2022 AHA Heart Failure Guidelines listing SGLT2i as first-line recommended agents for HF patients with T2DM. A real-world study simulating a target trial suggested that initiating SGLT2i within 3 days after discharge in patients with acute decompensated HF maximally reduces the composite endpoint of 1-year HF rehospitalization and cardiovascular death (OR=0.65 compared with delayed initiation), establishing early SGLT2i initiation as a key measure for improving long-term prognosis. Notably, although preclinical studies suggest potential improvements in myocardial energy metabolism, clinical trial evidence indicates this is not the primary mechanism for clinical benefit in

HFpEF, and the exact pathways require further investigation.

In HFrEF patients with comorbid T2DM, angiotensin receptor-neprilysin inhibitors (ARNI) demonstrate superiority over angiotensin-converting enzyme inhibitors (ACEI), not only more significantly reducing HF hospitalization and death risk but also providing modest glycemic improvement and potentially delaying insulin requirement. Studies have shown that combined ARNI and SGLT2i therapy produces synergistic "1+1>2" effects, outperforming monotherapy in improving cardiac function (LVEF, diastolic function e' , B-type natriuretic peptide), vascular endothelial function (flow-mediated vasodilation, nitric oxide), and suppressing neuroendocrine activation and inflammation. This evidence supports the combination of these two first-line agents acting on different pathways as an efficient strategy for managing HF and T2DM comorbidity to achieve comprehensive cardio-metabolic benefits.

4.1.2 Precision Application of Standard Medications Unless contraindicated, all HFrEF patients should receive β-blockers, as T2DM does not affect their efficacy in improving HF prognosis, and certain β-blockers (such as carvedilol) may provide additional benefits in improving myocardial metabolism. In elderly patients, treatment should start with low doses with close monitoring to avoid masking hypoglycemic sympathetic symptoms. Classic mineralocorticoid receptor antagonists (MRAs) such as spironolactone and eplerenone reduce mortality and rehospitalization in HF patients, with equivalent benefits in T2DM subgroups. Evidence shows that low-dose spironolactone (10-20 mg/day) for one year provides multiple improvements in cardiac, renal, and metabolic parameters in HFmrEF patients with T2DM, demonstrating good safety in elderly patients and those with CKD stage 3 or above, suggesting its application may extend beyond HFrEF and highlighting its value in this comorbid population.

The novel non-steroidal MRA finerenone demonstrates excellent cardiorenal protective effects in T2DM patients with CKD. A prespecified analysis of the FINEARTS-HF trial showed that finerenone significantly reduces cardiovascular events (particularly HF hospitalization) and renal disease progression risk. Its unique advantage lies in consistently reducing major cardiovascular risk in HFmrEF/HFpEF patients regardless of baseline glycemic status (normal, prediabetes, or established diabetes; interaction P=0.93), while significantly reducing new-onset diabetes risk by 24%. These findings indicate that finerenone not only improves outcomes in HF patients with T2DM but also serves as an effective preventive intervention for patients at risk for diabetes or HF, adding crucial evidence for its application throughout the management continuum of this comorbid population.

4.1.3 Supplementary Roles of Other Medications Diuretics are used to control volume status but require close monitoring of electrolytes and renal function in elderly patients. Vericiguat and ivabradine can be used in indicated HFrEF patients to reduce cardiovascular event risk or control heart rate, with

efficacy unaffected by diabetes status. In elderly patients with polypharmacy, attention must be paid to drug interactions and individualized selection.

4.2 Glucose Management Strategies Glucose-lowering drug selection must follow the principle of "HF safety first" while pursuing additional cardiorenal metabolic benefits. As previously mentioned, SGLT2i are glucose-lowering agents with exceptional HF benefits and should serve as the cornerstone of combination therapy.

4.2.1 Preferred Agents Glucagon-like peptide-1 receptor agonists (GLP-1 RA) have a neutral effect on HF rehospitalization risk but clearly reduce major adverse cardiovascular event (MACE) risk. For obese HFpEF patients, semaglutide has been shown to substantially improve HF-related symptoms and quality of life through significant weight reduction (STEP-HFpEF study). The SELECT study demonstrated that these benefits extend to non-obese patients and remain effective in patients already receiving SGLT2i, supporting the synergistic value of dual therapy. This body of clinical evidence provides new options for treating HFpEF, a phenotype common in elderly T2DM patients but lacking effective therapies. Additionally, the glucose-dependent insulinotropic polypeptide/GLP-1 dual receptor agonist tirzepatide shows exceptional potential in HFpEF treatment. Importantly, despite smaller weight reduction in T2DM patients, its benefits in HF outcomes and cardiac remodeling (reduction in left ventricular mass and pericardial fat) are comparable to those in non-diabetic patients, suggesting that the cardiovascular protective effects of these agents may be partially independent of weight loss, offering new perspectives and therapeutic weapons for HFpEF management.

4.2.2 Medications to Withhold or Avoid Metformin is safe in stable chronic HF elderly patients and may be associated with reduced mortality, remaining a first-line oral option, but should be withheld during acute decompensation. Insulin increases hypoglycemia risk and often worsens HF through sodium/water retention and weight gain, and should be reserved with minimal effective dosing, with early transition to oral agents with HF benefits once stable. Dipeptidyl peptidase-4 inhibitors have neutral overall cardiovascular effects, but saxagliptin is associated with increased HF hospitalization risk and should be avoided; other agents may be considered cautious second-line options. Sulfonylureas and glinides carry higher hypoglycemia risk and potential harm, making them suboptimal choices. Thiazolidinediones should be avoided due to clearly increased HF risk.

4.2.3 Simplification and Stabilization of Glycemic Control For elderly patients, particularly those who are frail or have multiple comorbidities, a "de-intensification" principle should be followed. Strict glycemic control (HbA1c $<7.0\%$) carries hypoglycemia risks that far outweigh minimal benefits. Guidelines recommend relaxing HbA1c targets to 7.0%-8.5%, with even more liberal

targets for those with limited life expectancy or frailty. Additionally, long-term glycemic variability may independently predict new-onset atrial fibrillation through mechanisms such as impaired cardiac autonomic regulation, suggesting that glycemic stability should gradually enter the field of vision of HF management. Beyond focusing on glycemic targets, efforts should be directed toward reducing glycemic fluctuations and achieving stable control.

4.3 Lifestyle Intervention and Multidisciplinary Team Management

4.3.1 Foundational Role of Lifestyle Intervention Sodium restriction (<5 g daily) is crucial for controlling volume status in these patients. For overweight/obese patients, gradual weight loss plans (targeting 5%-10% reduction) can significantly improve cardiac function and insulin sensitivity, though caution is needed regarding malnutrition and cachexia risk in advanced age patients who should maintain adequate protein intake. During stable periods, individualized exercise rehabilitation can improve cardiopulmonary function, muscle strength, and quality of life, with aerobic exercise as the main component supplemented by resistance training and close monitoring of exercise-induced symptoms.

4.3.2 Central Role of Multidisciplinary Teams (MDT) Given the complexity of the disease, establishing an MDT is fundamental to achieving "co-morbidity co-treatment" and "co-morbidity unified management," with MDT joint clinics being the core operational model. MDTs can simultaneously conduct comprehensive geriatric assessment covering disease status, cognitive function, mood, physical function, nutrition, and social support, thereby changing the current situation where each specialty clinic operates independently, reducing patient burden, and improving compliance. MDTs further coordinate HF and glucose-lowering therapies, optimize and simplify polypharmacy, and can provide continuous follow-up, education, and support from hospital to community/home, working with patients and families to establish individualized, patient-values-oriented treatment and quality-of-life goals.

The treatment of elderly patients with comorbid HF and T2DM has entered an era emphasizing "cardio-metabolic" comprehensive management, with multi-effect drugs such as SGLT2i, novel MRAs, and GLP-1 RA as cornerstones. The therapeutic goal is not to reduce glucose or BNP to specific numerical values, but rather to customize a long-term comprehensive management strategy for each elderly patient that balances efficacy, safety, and quality of life through the MDT model, ultimately breaking the "cardio-metabolic" vicious cycle and improving clinical outcomes.

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5. Future Directions

5.1 Generation of High-Quality Evidence for Elderly Comorbid Populations Future research should focus on conducting specialized clinical stud-

ies for elderly patients with comorbidities. The current priority is to fill the substantial evidence gap in this area, urgently requiring the design and implementation of large-scale prospective randomized controlled trials specifically targeting elderly populations (particularly those $ $75 years), frailty, and multiple comorbidities. These studies should not exclude such populations as in previous research, but rather should target them as core study subjects, incorporating comprehensive geriatric assessment indicators (such as frailty index, cognitive function, and polypharmacy) to provide direct and reliable high-level evidence for individualized management of this highly heterogeneous yet highly representative population.

5.2 Exploration of Therapeutic Targets Beyond Conventional Approaches Recent research on comorbidity pathophysiology is driving new models beyond conventional pharmacotherapy. Human umbilical cord blood-derived mesenchymal stem cells (UC-MSC) possess potent anti-inflammatory and anti-fibrotic effects, showing promise in early clinical trials for persistently improving glycemic control and β-cell function in T2DM patients. Endomyocardial injection of UC-MSC has been shown to improve cardiac remodeling and function and reduce cardiovascular event risk in HFrEF patients. Stem cell therapy is expanding its application to aging itself—the core driver of comorbidity—with preliminary studies showing that cell-based therapies and Senolytics targeting senescent cell clearance can improve frailty in elderly models and downregulate core mediators of "inflammaging," offering hope for fundamentally delaying comorbidity progression. Although these therapies require more evidence before clinical application, they mark a shift in intervention for HF and T2DM comorbidity from symptomatic management toward disease-modifying treatments targeting disease roots and shared pathological mechanisms (aging, chronic inflammation, etc.).

5.3 Empowerment Through Precision Medicine and Digital Health Traditional risk models have limited discriminatory ability in high-risk populations with comorbid T2DM. Precision risk prediction based on multi-omics represents another frontier for optimizing management. A study using the UK Biobank cohort demonstrated that machine learning algorithms integrating multi-omics data such as metabolomics to construct novel biomarker profiles can significantly improve prediction accuracy for cardiovascular events including HF in T2DM patients. Integrating such metabolomics-driven novel biomarkers into clinical prediction models promises earlier risk identification and more precise risk stratification for elderly T2DM patients with comorbidities, providing decision support for targeted intensive interventions and representing a key step toward precision prevention. Simultaneously, deep integration of digital health technologies (such as wearable devices, remote monitoring platforms, and AI-assisted decision-making) will enable continuous, dynamic patient management, effectively improving treatment adherence, optimizing medical resource allocation, and ultimately constructing a seamless integrated care network connecting

hospitals, communities, and homes.

Conclusion

The comorbidity of HF and T2DM in elderly populations represents a formidable clinical challenge, with complex bidirectional pathophysiological mechanisms exacerbated by the aging process. Clinical management must abandon the outdated specialty-based "single disease treatment" model and shift toward an individualized strategy based on the principle of "co-morbidity co-treatment," grounded in evidence-based medicine and implemented through multidisciplinary comprehensive management. The emergence of novel medications provides powerful tools for this approach. Looking forward, only by promoting clinical research dedicated to elderly comorbid populations, exploring cutting-edge fields such as cell therapy and aging-targeted interventions, and widely integrating digital health and integrated care models can we effectively address this growing public health challenge and ultimately improve clinical outcomes and quality of life for these patients.

Author Contributions

LAN Bo: Conceptualization and writing, revision of manuscript. WANG Zhenwei: Proposal and design of research, review of revised manuscript. LI Xiang: Collection and organization of research materials, drafting of manuscript. ZHANG Jinying: Manuscript revision, quality control. TANG Junnan: Manuscript review and editing, final version revision, overall responsibility for the manuscript.

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