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EARLY STRUCTURAL AND FUNCTIONAL CARDIAC CHANGES IN METABOLIC SYNDROME: FROM DIFFUSE MYOCARDIAL FIBROSIS TO HEART FAILURE WITH PRESERVED EJECTION FRACTION

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ABSTRACT

Background and Objective: Metabolic syndrome (MetS) affects approximately one-quarter of the global adult population and is increasingly recognized as a potent driver of subclinical cardiac remodeling that ultimately culminates in heart failure with preserved ejection fraction (HFpEF). Despite the well-established epidemiological association between MetS and HFpEF, the precise temporal sequence of early structural and functional cardiac alterations — particularly the role of diffuse myocardial fibrosis as a mechanistic bridge — remains incompletely characterized. The primary objective of this study was to comprehensively evaluate early cardiac structural and functional changes in patients with MetS who have not yet developed overt heart failure, with particular emphasis on quantifying diffuse myocardial fibrosis using cardiac magnetic resonance (CMR) T1 mapping and correlating these findings with echocardiographic indices of diastolic dysfunction.

Methods: This cross-sectional observational study enrolled 360 participants stratified into three groups: MetS without cardiovascular symptoms (n=140), MetS with evidence of diastolic dysfunction (n=120), and age- and sex-matched healthy controls (n=100). All participants underwent comprehensive transthoracic echocardiography with speckle-tracking strain analysis, CMR with native T1 mapping and extracellular volume (ECV) fraction quantification, and serum biomarker assessment including high-sensitivity cardiac troponin T (hs-cTnT), N-terminal pro-B-type natriuretic peptide (NT-proBNP), galectin-3, and soluble suppression of tumorigenicity 2 (sST2).

Results: Native T1 values and ECV fractions increased stepwise from healthy controls (1,018 ± 25 ms; 26.2 ± 2.1%) to asymptomatic MetS patients (1,058 ± 33 ms; 29.1 ± 3.2%) and MetS patients with diastolic dysfunction (1,082 ± 38 ms; 31.4 ± 3.8%; $p<0.001$ for all pairwise comparisons), indicating diffuse interstitial fibrosis even in the absence of clinical symptoms. Global longitudinal strain (GLS) was significantly impaired in both MetS groups despite preserved left ventricular ejection fraction (LVEF). ECV fraction demonstrated the strongest independent correlation with E/e' ratio ($r=0.72$, $p<0.001$) and was an independent predictor of diastolic dysfunction after multivariable adjustment (OR = 1.42 per 1% increase; AUC = 0.84). Galectin-3 levels were significantly elevated across both MetS

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groups and correlated positively with ECV fraction.

Conclusion: Diffuse myocardial fibrosis, detectable by CMR-derived ECV quantification, represents an early and potentially reversible structural hallmark of MetS-related cardiac remodeling that precedes and mechanistically contributes to the development of diastolic dysfunction and ultimately HFpEF. Integration of advanced imaging biomarkers with circulating fibrosis markers may enable earlier identification and targeted intervention in at-risk populations.

Keywords: metabolic syndrome, diffuse myocardial fibrosis, heart failure with preserved ejection fraction, extracellular volume fraction, diastolic dysfunction, T1 mapping, cardiac remodeling

1. INTRODUCTION

1.1. Relevance and Clinical Significance

Metabolic syndrome (MetS) — defined by the constellation of central obesity, insulin resistance, dyslipidemia, and arterial hypertension — has reached pandemic proportions, affecting an estimated 20–25% of the global adult population and exceeding 35% prevalence in individuals over the age of 60 (Saklayen, 2018). Beyond its well-characterized role as a risk multiplier for atherosclerotic cardiovascular disease and type 2 diabetes mellitus, MetS is now recognized as a potent and independent driver of adverse cardiac remodeling that operates through mechanisms distinct from coronary artery disease. Specifically, the metabolic milieu characteristic of MetS — encompassing chronic hyperinsulinemia, systemic low-grade inflammation, oxidative stress, and neurohormonal activation — directly promotes myocardial hypertrophy, interstitial fibrosis, microvascular dysfunction, and cardiomyocyte stiffening, collectively establishing the structural and functional substrate for heart failure with preserved ejection fraction (HFpEF) (Paulus & Tschöpe, 2013).

HFpEF currently accounts for more than half of all heart failure cases worldwide and represents one of the most formidable challenges confronting contemporary cardiovascular medicine (Borlaug, 2014). Unlike heart failure with reduced ejection fraction (HFrEF), for which evidence-based pharmacological therapies have demonstrated robust mortality reduction, HFpEF remains largely refractory to conventional neurohormonal blockade strategies. This therapeutic recalcitrance is attributable, at least in part, to the remarkable pathophysiological heterogeneity of HFpEF, which encompasses multiple distinct phenotypes driven by different comorbidity clusters (Shah et al., 2015). Among these phenotypic variants, the obesity-metabolic phenotype — characterized by MetS, visceral adiposity, and systemic inflammation — is one of the most common and has been characterized as a distinct HFpEF phenotype with specific hemodynamic and structural features (Obokata et al., 2017). Obesity is strongly linked to incident HFpEF in population-based cohorts (Pandey et al., 2017) and to adverse outcomes in patients with established HFpEF (Haass et al., 2011).

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Given the alarming epidemiological trajectory of MetS and the disproportionate burden of HFpEF in metabolically deranged populations, there exists an urgent clinical imperative to identify the earliest structural and functional cardiac changes that mark the transition from metabolic risk to overt cardiac dysfunction. Such identification would enable the implementation of targeted preventive strategies during a putatively reversible window of opportunity, before irreversible myocardial damage has been established.

1.2. Problem Statement

Despite substantial progress in understanding the epidemiological relationship between MetS and HFpEF, several critical knowledge gaps persist. The central unresolved question concerns the precise temporal and mechanistic sequence through which the metabolic perturbations of MetS translate into myocardial structural remodeling and, ultimately, clinical heart failure.

Conventional echocardiographic assessment, while invaluable for detecting established diastolic dysfunction and elevated filling pressures, possesses limited sensitivity for detecting the earliest stages of myocardial fibrosis — a process that may precede functional impairment by years or even decades. Left ventricular ejection fraction (LVEF), the most commonly utilized metric of systolic function, remains characteristically preserved throughout the entire natural history of MetS-related cardiac disease, providing false reassurance and delaying diagnosis until advanced stages of myocardial remodeling have been reached. Moreover, traditional diastolic function parameters — including E/A ratio, E/e' ratio, and left atrial volume index — exhibit substantial measurement variability and are influenced by loading conditions, heart rate, and age, complicating their interpretation in the MetS population (Nagueh et al., 2016).

Cardiac magnetic resonance (CMR) imaging, and specifically T1 mapping with extracellular volume (ECV) fraction quantification, has emerged as a transformative tool for the non-invasive assessment of diffuse myocardial fibrosis — a pathological process that is essentially invisible to conventional imaging modalities, including late gadolinium enhancement (LGE) CMR (Messroghli et al., 2017). Native T1 values and ECV fraction provide quantitative, reproducible, and histologically validated measures of myocardial tissue composition that can detect fibrotic changes at a subclinical stage, long before functional consequences become apparent. Importantly, ECV-quantified myocardial fibrosis has been shown to predict heart failure hospitalization and death across the full spectrum of ejection fraction (Schelbert et al., 2015). However, the systematic application of these advanced imaging techniques to characterize the full spectrum of cardiac remodeling in MetS — from the earliest subclinical fibrotic changes through to established diastolic dysfunction — has not been comprehensively undertaken.

1.3. Literature Review

The pathogenesis of myocardial fibrosis in MetS is multifactorial and involves the convergence of several interconnected molecular pathways. Insulin resistance, the metabolic hallmark of MetS, promotes myocardial fibrosis through multiple mechanisms:

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direct stimulation of cardiac fibroblast proliferation and collagen synthesis via activation of the transforming growth factor-beta (TGF-β) signaling cascade; enhancement of the renin-angiotensin-aldosterone system (RAAS) activity, which drives both myocyte hypertrophy and extracellular matrix expansion; and promotion of advanced glycation end-product (AGE) formation, which cross-links collagen fibers and increases myocardial stiffness (Cavalera et al., 2014).

Systemic low-grade inflammation, a cardinal feature of MetS mediated primarily by visceral adipose tissue-derived adipokines and proinflammatory cytokines (interleukin-6, tumor necrosis factor-alpha, leptin), activates coronary microvascular endothelial cells, inducing the expression of adhesion molecules and reactive oxygen species that shift the balance of cardiomyocyte signaling toward a pro-hypertrophic and pro-fibrotic state (Paulus & Tschöpe, 2013). This "systemic microvascular inflammation" paradigm, articulated most comprehensively by Paulus and Tschöpe (2013), posits that comorbidity-driven coronary microvascular endothelial inflammation is the central pathophysiological mechanism linking MetS to HFpEF — a conceptual framework that has gained substantial empirical support in subsequent investigations.

Several imaging studies have provided cross-sectional evidence of increased myocardial fibrosis in MetS and its individual components. Using CMR, Rider and colleagues (2013) demonstrated that obesity is associated with concentric left ventricular remodeling, with sex-specific differences in the remodeling pattern. Levelt and colleagues (2016) extended these observations to patients with type 2 diabetes, showing that concentric remodeling is accompanied by impaired myocardial energetics assessed by phosphorus-31 magnetic resonance spectroscopy and by myocardial steatosis, even in the absence of coronary artery disease. Similarly, Ernande and colleagues (2014) utilized speckle-tracking echocardiography to demonstrate impaired GLS in diabetic patients with preserved LVEF, establishing subclinical systolic dysfunction as an early functional consequence of metabolic cardiac disease.

However, significant limitations characterize the existing literature. First, most studies have focused on individual MetS components (obesity, diabetes, hypertension) in isolation, rather than examining MetS as an integrated pathophysiological entity. Second, the simultaneous assessment of multiple imaging modalities (echocardiography and CMR) alongside circulating fibrosis biomarkers in a single well-characterized MetS cohort has rarely been undertaken. Third, the correlation between CMR-derived fibrosis indices and echocardiographic diastolic function parameters in MetS patients across different stages of cardiac remodeling — from asymptomatic subclinical disease to established diastolic dysfunction — remains insufficiently defined.

1.4. Study Objectives and Hypotheses

Based on the identified research gaps, the following objectives and hypotheses were formulated:

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Primary objective: To comprehensively characterize and compare early structural and functional cardiac changes across the spectrum of MetS-related cardiac remodeling using multimodality imaging (echocardiography and CMR) and circulating biomarkers.

Research hypotheses:

H_1: Patients with MetS, even in the absence of cardiovascular symptoms, demonstrate significantly elevated CMR-derived markers of diffuse myocardial fibrosis (native T1 values and ECV fraction) compared to age- and sex-matched healthy controls.

H_2: The degree of diffuse myocardial fibrosis, quantified by ECV fraction, is independently and significantly correlated with echocardiographic indices of diastolic dysfunction (E/e' ratio, left atrial volume index).

H_3: Circulating biomarkers of fibrosis and myocardial stress (galectin-3, sST2, hs-cTnT, NT-proBNP) are elevated in MetS patients and correlate with the severity of CMR-detected fibrosis.

2. METHODS

2.1. Study Design and Setting

This investigation was designed as a prospective cross-sectional observational study conducted at the Cardiovascular Imaging Research Center of a tertiary university hospital between March 2021 and September 2024. The study protocol was developed in accordance with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines and the Declaration of Helsinki ethical principles for medical research involving human subjects.

2.2. Participants and Group Allocation

A total of 360 participants were enrolled and stratified into three groups:

Group 1 — MetS without diastolic dysfunction (MetS-Asympt): 140 patients meeting the harmonized International Diabetes Federation (IDF)/American Heart Association (AHA) 2009 consensus criteria for MetS (presence of ≥3 of 5 components: waist circumference ≥102 cm in men / ≥88 cm in women; triglycerides ≥150 mg/dL; HDL-cholesterol <40 mg/dL in men / <50 mg/dL in women; blood pressure ≥130/85 mmHg or on antihypertensive therapy; fasting glucose ≥100 mg/dL or on glucose-lowering therapy) (Alberti et al., 2009), with no evidence of diastolic dysfunction on baseline echocardiography and no cardiovascular symptoms.

Group 2 — MetS with diastolic dysfunction (MetS-DD): 120 patients meeting the same MetS criteria and additionally demonstrating grade I or grade II diastolic dysfunction according to the 2016 ASE/EACVI guidelines (Nagueh et al., 2016), with LVEF ≥ 50% and no prior heart failure diagnosis.

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Group 3 — Healthy controls (HC): 100 age- and sex-matched individuals without MetS components, cardiovascular disease, diabetes, hypertension, or significant comorbidities.

Exclusion criteria (all groups): known coronary artery disease (prior myocardial infarction, revascularization, or ≥50% stenosis on coronary angiography or CT angiography); primary cardiomyopathy or valvular heart disease (moderate or greater severity); atrial fibrillation; estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m² (contraindication for gadolinium-based contrast); implanted metallic devices incompatible with MRI; LVEF < 50%; and established heart failure diagnosis.

2.3. Comprehensive Transthoracic Echocardiography

All participants underwent comprehensive two-dimensional (2D) and Doppler transthoracic echocardiography performed by experienced sonographers (Level III accreditation) using commercially available ultrasound systems (Vivid E95, GE Healthcare, or EPIQ CVx, Philips Healthcare). Standard measurements included: LV dimensions and wall thickness (M-mode), LV mass index (LVMI, calculated by the Devereux formula and indexed to body surface area), relative wall thickness (RWT), left atrial volume index (LAVI, biplane method of discs), LVEF (biplane Simpson's method), mitral inflow velocities (E-wave, A-wave, E/A ratio, deceleration time), tissue Doppler imaging (TDI)-derived septal and lateral e' velocities, and E/e' ratio (averaged septal-lateral). Diastolic function was graded according to the 2016 ASE/EACVI recommendations. Tricuspid regurgitation velocity and estimated pulmonary artery systolic pressure were recorded when available.

Speckle-tracking echocardiography (STE): 2D speckle-tracking analysis was performed offline using dedicated vendor-specific software (EchoPAC, GE Healthcare) to derive global longitudinal strain (GLS) from apical four-chamber, two-chamber, and three-chamber views. GLS values were expressed as negative percentages, with less negative values indicating impaired longitudinal function. Intra- and inter-observer variability for GLS measurements was assessed in a random subset of 30 participants, yielding intraclass correlation coefficients (ICC) of 0.93 and 0.89, respectively.

2.4. Cardiac Magnetic Resonance Imaging

CMR was performed on a 3.0-Tesla scanner (MAGNETOM Prisma, Siemens Healthineers, Erlangen, Germany) using a 32-channel phased-array cardiac coil. The standardized CMR protocol included:

Cine imaging: Balanced steady-state free precession (bSSFP) cine sequences were acquired in short-axis stack (contiguous slices from base to apex) and standard long-axis views (2-chamber, 3-chamber, 4-chamber) for volumetric analysis. LV end-diastolic volume (LVEDV), end-systolic volume (LVESV), stroke volume, LVEF, and LV mass were quantified using semi-automated contouring software (CVI42, Circle Cardiovascular Imaging, Calgary, Canada).

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Native T1 mapping: Modified Look-Locker Inversion Recovery (MOLLI) sequences (5(3)3 scheme) were acquired at basal, mid-ventricular, and apical short-axis levels prior to contrast administration. T1 maps were generated inline, and native T1 values were measured by placing regions of interest (ROIs) within the mid-myocardial layer of the interventricular septum, carefully avoiding the blood pool and epicardial borders.

Post-contrast T1 mapping and ECV quantification: Post-contrast MOLLI sequences (4(1)3(1)2 scheme) were acquired 15–20 minutes after intravenous administration of a gadolinium-based contrast agent (gadobutrol, 0.1 mmol/kg, Gadovist®, Bayer Healthcare). ECV fraction was calculated using the standard formula: ECV = (1 − hematocrit) × [(1/T1 myocardium post-contrast − 1/T1 myocardium native) / (1/T1 blood post-contrast − 1/T1 blood native)]. Hematocrit values were obtained from venous blood samples drawn within 24 hours of the CMR examination.

Late gadolinium enhancement (LGE): Phase-sensitive inversion recovery (PSIR) sequences were acquired 10–15 minutes post-contrast to detect focal myocardial scar/fibrosis. LGE images were assessed qualitatively by two experienced CMR readers blinded to clinical data.

2.5. Serum Biomarker Assessment

Fasting venous blood samples were collected from all participants on the morning of the imaging assessments. The following biomarkers were analyzed:

- **High-sensitivity cardiac troponin T (hs-cTnT):** Elecsys® assay (Roche Diagnostics), limit of detection 3 ng/L;
- **NT-proBNP:** Elecsys® assay (Roche Diagnostics);
- **Galectin-3:** ELISA (BG Medicine);
- **Soluble ST2 (sST2):** Presage® ST2 assay (Critical Diagnostics);
- **High-sensitivity C-reactive protein (hs-CRP):** immunoturbidimetric assay;
- **Fasting insulin and HOMA-IR:** calculated as [fasting insulin (μU/mL) × fasting glucose (mmol/L)] / 22.5.

2.6. Statistical Analysis

Statistical analyses were performed using SPSS version 28.0 (IBM Corp.) and R version 4.3.1 (R Foundation for Statistical Computing). Continuous variables were expressed as mean ± SD or median (IQR) and compared using one-way ANOVA with Tukey's post-hoc test or Kruskal-Wallis test with Dunn's post-hoc test, as appropriate. Categorical variables were expressed as n (%) and compared using the chi-square test. Correlations between continuous variables were assessed using Pearson's or Spearman's correlation coefficients. Multivariable linear regression analysis was performed to identify independent determinants of ECV fraction and E/e' ratio, adjusting for age, sex, BMI, systolic blood pressure, HOMA-IR, and hs-CRP. Multivariable logistic regression was employed to identify independent predictors of diastolic dysfunction. Receiver operating characteristic (ROC) curve analysis was performed to determine the discriminative

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capacity of ECV fraction and biomarkers for detecting diastolic dysfunction. A two-tailed p-value < 0.05 was considered statistically significant.

2.7. Ethical Approval

The study protocol was approved by the Institutional Ethics Committee (approval number: CVR-IRB-2021/042). Written informed consent was obtained from all participants prior to enrollment.

3. RESULTS

3.1. Baseline Characteristics

The three groups were well-matched for age (HC: 51.3 ± 9.4 years; MetS-Asympt: 52.8 ± 10.1 years; MetS-DD: 54.6 ± 9.8 years; p = 0.062) and sex distribution (male proportion: HC 48%, MetS-Asympt 52.1%, MetS-DD 55.8%; p = 0.434). As expected, both MetS groups exhibited significantly higher BMI (HC: 24.1 ± 2.8; MetS-Asympt: 31.6 ± 4.2; MetS-DD: 33.4 ± 4.8 kg/m²; p < 0.001), waist circumference, fasting glucose, HOMA-IR, triglycerides, systolic blood pressure, and hs-CRP compared to healthy controls (all p < 0.001). The MetS-DD group demonstrated a significantly higher number of MetS components (4.2 ± 0.7 vs. 3.6 ± 0.8 in MetS-Asympt, p < 0.001) and longer estimated duration of MetS diagnosis (Table 1).

Table 1. Baseline demographic, metabolic, and clinical characteristics of study groups

Parameter	HC (n = 100)	MetS-Asympt (n = 140)	MetS-DD (n = 120)	p-value
Age, years	51.3 ± 9.4	52.8 ± 10.1	54.6 ± 9.8	0.062
Male sex, %	48.0	52.1	55.8	0.434
BMI, kg/m²	24.1 ± 2.8	31.6 ± 4.2	33.4 ± 4.8	< 0.001
hs-CRP, mg/L	0.8 (0.4–1.4)	3.2 (1.8–5.4)	4.8 (2.6–7.2)	< 0.001
Number of MetS components	—	3.6 ± 0.8	4.2 ± 0.7	< 0.001†

Data are presented as mean ± SD, median (IQR), or %. † MetS-Asympt vs. MetS-DD. Waist circumference, fasting glucose, HOMA-IR, triglycerides, and systolic blood pressure were also significantly higher in both MetS groups than in controls (all p < 0.001). HC — healthy controls; MetS-Asympt — metabolic syndrome without diastolic dysfunction; MetS-DD — metabolic syndrome with diastolic dysfunction.

3.2. Echocardiographic Findings

Left ventricular geometry: LVMI was significantly elevated in both MetS groups compared to controls (HC: 78.4 ± 12.3 g/m²; MetS-Asympt: 96.2 ± 15.8 g/m²; MetS-DD: 112.5 ± 18.4 g/m²; p < 0.001). Concentric remodeling (RWT > 0.42 with normal LVMI)

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was present in 34.3% of MetS-Asympt patients, while concentric hypertrophy (RWT > 0.42 with elevated LVMI) was observed in 48.3% of MetS-DD patients. Among healthy controls, normal LV geometry was present in 91.0%.

Systolic function: LVEF was preserved and comparable across all three groups (HC: 62.4 ± 4.1%; MetS-Asympt: 61.8 ± 4.5%; MetS-DD: 60.2 ± 5.1%; p = 0.198). In contrast, GLS was progressively impaired across the spectrum: HC: −20.8 ± 1.6%; MetS-Asympt: −18.2 ± 2.1%; MetS-DD: −16.1 ± 2.4% (p < 0.001 for trend; all pairwise comparisons significant at p < 0.01). Notably, 38.6% of MetS-Asympt patients and 71.7% of MetS-DD patients exhibited abnormal GLS (defined as less negative than −18%), despite universally preserved LVEF.

Diastolic function: As expected by group definition, the MetS-DD group demonstrated significantly elevated E/e' ratio (HC: 7.2 ± 1.8; MetS-Asympt: 9.4 ± 2.3; MetS-DD: 13.8 ± 3.1; p < 0.001), increased LAVI (HC: 24.6 ± 5.1 mL/m²; MetS-Asympt: 29.8 ± 6.4 mL/m²; MetS-DD: 38.2 ± 7.8 mL/m²; p < 0.001), and reduced septal e' velocity (HC: 10.2 ± 2.1 cm/s; MetS-Asympt: 8.1 ± 1.9 cm/s; MetS-DD: 6.3 ± 1.7 cm/s; p < 0.001). However, it is particularly noteworthy that the MetS-Asympt group, despite not meeting criteria for diastolic dysfunction, already demonstrated significantly abnormal diastolic parameters compared to controls, suggesting an early, transitional stage of diastolic impairment (Table 2).

Table 2. Echocardiographic structural and functional parameters across study groups

Parameter	HC (n = 100)	MetS-Asympt (n = 140)	MetS-DD (n = 120)	p-value
LVMI, g/m²	78.4 ± 12.3	96.2 ± 15.8	112.5 ± 18.4	< 0.001
LVEF, %	62.4 ± 4.1	61.8 ± 4.5	60.2 ± 5.1	0.198
GLS, %	−20.8 ± 1.6	−18.2 ± 2.1	−16.1 ± 2.4	< 0.001*
E/e' ratio	7.2 ± 1.8	9.4 ± 2.3	13.8 ± 3.1	< 0.001
LAVI, mL/m²	24.6 ± 5.1	29.8 ± 6.4	38.2 ± 7.8	< 0.001
Septal e' velocity, cm/s	10.2 ± 2.1	8.1 ± 1.9	6.3 ± 1.7	< 0.001

*Data are presented as mean ± SD or n (%). * p for trend; all pairwise comparisons p < 0.01. GLS — global longitudinal strain; LAVI — left atrial volume index; LVEF — left ventricular ejection fraction; LVMI — left ventricular mass index. HC — healthy controls; MetS-Asympt — metabolic syndrome without diastolic dysfunction; MetS-DD — metabolic syndrome with diastolic dysfunction.*

3.3. Cardiac Magnetic Resonance Findings

Volumetric and mass data: CMR-derived LVEDV index did not differ significantly among groups (p = 0.31). CMR-derived LV mass index demonstrated the same progressive elevation observed on echocardiography (HC: 56.2 ± 9.8 g/m²; MetS-

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Asympt: 72.4 ± 12.6 g/m²; MetS-DD: 86.8 ± 15.3 g/m²; p < 0.001). LVEF by CMR was preserved in all groups.

Native T1 values: Septal native T1 values demonstrated a stepwise increase across the three groups: HC: 1,018 ± 25 ms; MetS-Asympt: 1,058 ± 33 ms; MetS-DD: 1,082 ± 38 ms (p < 0.001 for overall comparison; HC vs. MetS-Asympt: p < 0.001; MetS-Asympt vs. MetS-DD: p < 0.001). This progressive elevation strongly suggests an incremental burden of diffuse myocardial fibrosis and/or edema along the MetS remodeling spectrum.

Extracellular volume (ECV) fraction: ECV fraction exhibited a strikingly similar pattern of progressive elevation: HC: 26.2 ± 2.1%; MetS-Asympt: 29.1 ± 3.2%; MetS-DD: 31.4 ± 3.8% (p < 0.001 for overall comparison; all pairwise comparisons p < 0.001). The magnitude of ECV elevation in the MetS-DD group (approximately 5.2 percentage points above controls) is consistent with a moderate burden of diffuse interstitial fibrosis and is comparable to values reported in histologically confirmed myocardial fibrosis in other disease states.

Late gadolinium enhancement (LGE): Focal LGE was detected in only 8 patients across the entire cohort (2.2%): 2 in HC (non-ischemic pattern, likely incidental), 3 in MetS-Asympt, and 3 in MetS-DD. The low prevalence of focal LGE underscores that the predominant pattern of fibrosis in MetS is diffuse and interstitial, rather than focal replacement fibrosis, and further validates the necessity of T1 mapping and ECV quantification for its detection (Table 3).

Table 3. CMR-derived structural and tissue characterization parameters

Parameter	HC (n = 100)	MetS-Asympt (n = 140)	MetS-DD (n = 120)	p-value
LV mass index, g/m²	56.2 ± 9.8	72.4 ± 12.6	86.8 ± 15.3	< 0.001
Native T1 (septal), ms	1,018 ± 25	1,058 ± 33	1,082 ± 38	< 0.001
ECV fraction, %	26.2 ± 2.1	29.1 ± 3.2	31.4 ± 3.8	< 0.001

Data are presented as mean ± SD or n (%). For native T1 and ECV, all pairwise comparisons p < 0.001. LVEDV index did not differ among groups (p = 0.31); focal LGE was found in 2 (2.0%), 3 (2.1%), and 3 (2.5%) participants, respectively. CMR performed at 3.0 T. ECV — extracellular volume; LGE — late gadolinium enhancement; LVEDV — left ventricular end-diastolic volume. HC — healthy controls; MetS-Asympt — metabolic syndrome without diastolic dysfunction; MetS-DD — metabolic syndrome with diastolic dysfunction.

3.4. Circulating Biomarker Profile

hs-cTnT: A progressive elevation was observed: HC: 4.2 (3.1–5.8) ng/L; MetS-Asympt: 7.8 (5.4–11.2) ng/L; MetS-DD: 12.4 (8.6–16.8) ng/L (p < 0.001). Although values remained below the conventional 99th percentile for myocardial infarction diagnosis in most patients, the elevation reflects ongoing low-grade myocardial injury.

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NT-proBNP: HC: 38 (22–64) pg/mL; MetS-Asympt: 62 (34–98) pg/mL; MetS-DD: 148 (86–245) pg/mL ($p < 0.001$). Notably, NT-proBNP values in the MetS-Asympt group remained largely within the normal range, limiting the sensitivity of this biomarker for detecting early remodeling stages.

Galectin-3: HC: 9.4 ± 2.8 ng/mL; MetS-Asympt: 14.6 ± 4.2 ng/mL; MetS-DD: 19.8 ± 5.6 ng/mL ($p < 0.001$ for all pairwise comparisons). Galectin-3, a marker specifically linked to fibroblast activation and collagen turnover, demonstrated the most consistent and progressive elevation across the MetS spectrum among all biomarkers assessed.

sST2: HC: 18.4 ± 6.2 ng/mL; MetS-Asympt: 24.8 ± 8.4 ng/mL; MetS-DD: 32.6 ± 10.8 ng/mL ($p < 0.001$).

hs-CRP: HC: 0.8 (0.4–1.4) mg/L; MetS-Asympt: 3.2 (1.8–5.4) mg/L; MetS-DD: 4.8 (2.6–7.2) mg/L ($p < 0.001$), confirming the presence of systemic low-grade inflammation in MetS (Table 4).

Table 4. Circulating biomarker levels across study groups

Parameter	HC (n = 100)	MetS-Asympt (n = 140)	MetS-DD (n = 120)	p-value
hs-cTnT, ng/L	4.2 (3.1–5.8)	7.8 (5.4–11.2)	12.4 (8.6–16.8)	< 0.001
NT-proBNP, pg/mL	38 (22–64)	62 (34–98)	148 (86–245)	< 0.001
Galectin-3, ng/mL	9.4 ± 2.8	14.6 ± 4.2	19.8 ± 5.6	< 0.001†
sST2, ng/mL	18.4 ± 6.2	24.8 ± 8.4	32.6 ± 10.8	< 0.001
hs-CRP, mg/L	0.8 (0.4–1.4)	3.2 (1.8–5.4)	4.8 (2.6–7.2)	< 0.001

Data are presented as mean ± SD or median (IQR). † All pairwise comparisons. hs-cTnT — high-sensitivity cardiac troponin T; NT-proBNP — N-terminal pro-B-type natriuretic peptide; sST2 — soluble suppression of tumorigenicity 2; hs-CRP — high-sensitivity C-reactive protein. HC — healthy controls; MetS-Asympt — metabolic syndrome without diastolic dysfunction; MetS-DD — metabolic syndrome with diastolic dysfunction.

3.5. Correlations and Multivariable Analyses

ECV fraction demonstrated significant positive correlations with E/e' ratio ($r = 0.72$, $p < 0.001$), LAVI ($r = 0.64$, $p < 0.001$), LVMI ($r = 0.58$, $p < 0.001$), galectin-3 ($r = 0.68$, $p < 0.001$), sST2 ($r = 0.54$, $p < 0.001$), HOMA-IR ($r = 0.52$, $p < 0.001$), and hs-CRP ($r = 0.46$, $p < 0.001$). Conversely, ECV fraction demonstrated a significant inverse correlation with GLS ($r = -0.65$, $p < 0.001$) and septal e' velocity ($r = -0.61$, $p < 0.001$).

Multivariable linear regression analysis, with ECV fraction as the dependent variable and adjustment for age, sex, BMI, systolic blood pressure, HOMA-IR, hs-CRP, and galectin-3, identified HOMA-IR ($\beta = 0.28$, $p < 0.001$), galectin-3 ($\beta = 0.32$, $p < 0.001$), and systolic blood pressure ($\beta = 0.19$, $p = 0.004$) as independent determinants of ECV

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fraction. Notably, BMI was not independently associated with ECV after adjustment for HOMA-IR, suggesting that insulin resistance — rather than adiposity per se — is the primary metabolic driver of myocardial fibrosis.

Multivariable logistic regression analysis identified ECV fraction (OR = 1.42 per 1% increase; 95% CI: 1.24–1.63; $p < 0.001$), HOMA-IR (OR = 1.18; 95% CI: 1.08–1.29; $p < 0.001$), and LVMI (OR = 1.03; 95% CI: 1.01–1.05; $p = 0.009$) as independent predictors of diastolic dysfunction. ROC curve analysis demonstrated that ECV fraction achieved an area under the curve (AUC) of 0.84 (95% CI: 0.79–0.89) for discriminating between MetS patients with and without diastolic dysfunction, with an optimal cutoff value of 29.5% (sensitivity 78%, specificity 81%).

4. DISCUSSION

4.1. Interpretation of Key Findings

The present study provides comprehensive multimodality evidence that metabolic syndrome induces a progressive continuum of structural and functional cardiac alterations that begins with diffuse interstitial myocardial fibrosis, progresses through subclinical systolic and diastolic impairment detectable by advanced imaging techniques, and ultimately culminates in overt diastolic dysfunction — the functional hallmark of HFpEF. Several key findings merit detailed discussion.

The demonstration of significantly elevated native T1 values and ECV fractions in MetS patients without cardiovascular symptoms (Group 1) compared to healthy controls represents perhaps the most clinically consequential finding of this investigation. This observation confirms our first hypothesis (H_1) and provides direct evidence that diffuse myocardial fibrosis is established at a very early stage of MetS-related cardiac disease — a stage at which conventional echocardiographic parameters of diastolic function may still appear relatively normal and at which patients are entirely asymptomatic. This finding is concordant with previous CMR studies that described concentric remodeling and metabolic alterations of the myocardium in obesity and type 2 diabetes (Rider et al., 2013; Levelt et al., 2016), and extends them by demonstrating tissue-level evidence of diffuse interstitial fibrosis in patients with the full metabolic syndrome phenotype.

The strong independent correlation between ECV fraction and E/e' ratio ($r = 0.72$), confirmed by multivariable logistic regression analysis identifying ECV fraction as an independent predictor of diastolic dysfunction (OR = 1.42 per 1% increase), validates our second hypothesis (H_2) and provides mechanistic insight into the structural basis of diastolic impairment in MetS. Expansion of the myocardial extracellular matrix through collagen deposition increases passive myocardial stiffness, impairs ventricular relaxation, and elevates LV filling pressures — precisely the hemodynamic derangements that define diastolic dysfunction (Zile et al., 2015). This quantitative structure-function relationship has important therapeutic implications: interventions capable of attenuating or reversing myocardial fibrosis may be expected to improve diastolic function and, potentially, prevent the progression to HFpEF.

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The progressive impairment of GLS across the MetS spectrum (HC: −20.8% → MetS-Asympt: −18.2% → MetS-DD: −16.1%), despite universally preserved LVEF, corroborates the findings of Ernande and colleagues (2014) and underscores the critical importance of myocardial strain imaging in detecting subclinical systolic dysfunction. GLS impairment likely reflects the deleterious effects of interstitial fibrosis on longitudinal myocardial fiber mechanics, as subendocardial fibers — which are predominantly oriented longitudinally and are most vulnerable to metabolic injury — are disproportionately affected in the early stages of disease. This finding reinforces the growing consensus that LVEF is an insensitive marker of myocardial health in the context of concentric remodeling and should not be relied upon as the sole metric of cardiac function in MetS patients.

4.2. Role of Circulating Biomarkers

The progressive elevation of galectin-3 across the MetS spectrum, and its strong correlation with ECV fraction ($r = 0.68$), supports our third hypothesis (H_3) and aligns with the known biological role of galectin-3 as a mediator and biomarker of cardiac fibrosis. Galectin-3 is secreted by activated macrophages and fibroblasts within the myocardium, where it promotes fibroblast proliferation, collagen deposition, and extracellular matrix remodeling (de Boer et al., 2009). Importantly, galectin-3 has been identified as a prognostically significant biomarker in established HFpEF (de Boer et al., 2009), and our data suggest that its elevation precedes the development of overt heart failure, potentially serving as an early circulating signal of myocardial fibrogenesis in MetS.

The observation that NT-proBNP levels in the MetS-Asympt group remained largely within the normal range despite already elevated ECV fractions and impaired GLS highlights a critical limitation of natriuretic peptide-based screening strategies in the MetS population. NT-proBNP is primarily a marker of myocardial wall stress secondary to elevated filling pressures and volume overload; in the early stages of MetS-related remodeling — when fibrosis is present but filling pressures remain only mildly elevated — NT-proBNP may lack the sensitivity to detect subclinical disease. This observation is consistent with the well-recognized "natriuretic peptide handicap" described in obese patients, in whom adipose tissue-mediated clearance of natriuretic peptides results in disproportionately low circulating levels relative to the degree of cardiac dysfunction (Madamanchi et al., 2014).

4.3. Mechanistic Insights: From Fibrosis to HFpEF

Integrating the findings of this study with the existing pathophysiological framework, we propose a refined model of the transition from MetS to HFpEF. In the earliest stage (represented by our MetS-Asympt group), insulin resistance and systemic inflammation drive low-grade, diffuse interstitial fibrosis that is detectable by ECV quantification and accompanied by subclinical longitudinal dysfunction (impaired GLS) but remains insufficient to produce hemodynamically significant diastolic impairment. As the metabolic insult persists and intensifies — with progressive accumulation of

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extracellular collagen, cardiomyocyte hypertrophy, titin isoform switching toward the stiffer N2B isoform, and coronary microvascular rarefaction — passive myocardial stiffness increases sufficiently to impair ventricular relaxation and elevate filling pressures, manifesting as echocardiographic diastolic dysfunction (our MetS-DD group). In the final stage, sustained elevation of filling pressures provokes left atrial remodeling (dilatation and fibrosis), pulmonary venous congestion, and ultimately the clinical syndrome of HFpEF.

This model is consistent with the hemodynamic findings of Obokata and colleagues (2017), who demonstrated that obese HFpEF patients exhibit a unique phenotype characterized by greater biventricular remodeling, more severe diastolic dysfunction, and more pronounced exercise-induced elevation of filling pressures compared to non-obese HFpEF patients. Our study extends their observations by demonstrating that the structural substrate for this hemodynamic phenotype — diffuse myocardial fibrosis — is already established years before the clinical manifestation of heart failure.

4.4. Clinical Implications

The findings carry several important clinical implications. First, CMR T1 mapping and ECV quantification should be considered as part of the cardiovascular risk assessment in high-risk MetS patients, particularly those with multiple MetS components, elevated galectin-3, or borderline diastolic function parameters. Second, the identification of HOMA-IR as an independent determinant of ECV fraction reinforces the potential role of insulin-sensitizing therapies — including SGLT2 inhibitors, GLP-1 receptor agonists, and metformin — not merely as glucose-lowering agents but as potential antifibrotic therapies with the capacity to attenuate myocardial remodeling. Notably, the EMPEROR-Preserved trial demonstrated that empagliflozin reduces the composite endpoint of cardiovascular death and heart failure hospitalization in HFpEF patients, (Anker et al., 2021), and a mechanistic rationale has been proposed for combining inhibitors of aldosterone, neprilysin, and SGLT2 in obesity-related HFpEF (Packer & Kitzman, 2018). Third, the earlier and more consistent elevation of galectin-3 compared with NT-proBNP in asymptomatic MetS suggests that a multimarker strategy incorporating fibrosis-specific biomarkers may enhance the sensitivity of screening approaches; this hypothesis requires formal testing of diagnostic performance.

4.5. Limitations

Several limitations warrant acknowledgment. First, the cross-sectional design precludes definitive establishment of temporal causality between diffuse fibrosis and subsequent diastolic dysfunction; prospective longitudinal studies are needed to confirm the proposed sequence. Second, ECV fraction, while histologically validated in other disease states, was not corroborated by endomyocardial biopsy in the present study, and elevated ECV could theoretically reflect myocardial edema in addition to fibrosis. Third, the single-center design and predominantly Caucasian and Central Asian study population may limit generalizability to other ethnic groups. Fourth, the use of 3.0-Tesla CMR, while providing superior signal-to-noise ratio, may produce T1 values that are not directly

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comparable to those obtained at 1.5 Tesla, necessitating field strength-specific reference ranges. Fifth, the MetS-Asympt group was defined by the absence of echocardiographic diastolic dysfunction, but subtle hemodynamic abnormalities detectable only during exercise stress testing may have been missed.

5. CONCLUSION

This comprehensive multimodality investigation demonstrates that metabolic syndrome induces a progressive continuum of cardiac structural and functional changes, beginning with diffuse interstitial myocardial fibrosis — detectable by CMR-derived ECV quantification — that is already present in asymptomatic individuals with MetS and that mechanistically underlies the subsequent development of diastolic dysfunction and the clinical syndrome of HFpEF. Key findings include: (1) significant elevation of native T1 values and ECV fractions in MetS patients compared to healthy controls, even in the absence of symptoms or conventional echocardiographic abnormalities; (2) a strong and independent correlation between ECV fraction and indices of diastolic function, establishing diffuse fibrosis as a structural determinant of diastolic impairment; (3) progressive impairment of GLS despite preserved LVEF, confirming subclinical systolic dysfunction as an early functional hallmark of MetS-related cardiac disease; and (4) elevation of galectin-3 as a circulating biomarker of myocardial fibrogenesis that may complement imaging-based assessment.

These findings carry substantial implications for the early detection, risk stratification, and therapeutic targeting of MetS-related cardiac remodeling. The integration of advanced CMR tissue characterization with circulating fibrosis biomarkers offers a powerful approach for identifying at-risk individuals during a potentially reversible window of subclinical disease, before the irreversible structural and functional changes characteristic of established HFpEF have been consolidated.

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