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Growth Differentiation Factor-15 and Cardiovascular Diseases: Biology, Clinical Implications, and Future Outlook

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SOUHRN

Růstový diferenciační faktor-15 (growth differentiation factor-15, GDF-15) je cytokin reagující na stres a spojovaný se zánětem, oxidačním stresem, metabolickou dysfunkcí a s poškozením tkání. V posledních 20 letech získal postavení významného biomarkeru u několika kardiovaskulárních onemocnění, jako jsou srdeční selhání, ischemická choroba srdeční, akutní koronární syndromy, vaskulární plicní onemocnění, arytmie, a u kardiometabolických onemocnění. Zvýšené hodnoty cirkulujícího GDF-15 předpovídají mortalitu, hospitalizaci pro srdeční selhání, opakované ischemické příhody a pravděpodobnost krvácení. Tento přehled shrnuje poznatky o biologii a patofyziologii GDF-15, jeho využití v diagnostice a prognostice, i uplatnění v léčbě a přináší i kritický pohled na současné mezery v důkazech a požadavky na další výzkum.

Keywords:
Cardiovascular diseases
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ABSTRACT

Growth Differentiation Factor-15 (GDF-15) is a cytokine responsive to stress, linked to inflammation, oxidative stress, metabolic dysfunction, and tissue damage. In the past twenty years, it has become a significant biomarker in several cardiovascular diseases (CVDs), such as heart failure (HF), coronary artery disease, acute coronary syndromes, pulmonary vascular disease, arrhythmias, and cardiometabolic disorders. Increased circulating GDF-15 levels forecast mortality, hospitalisation due to HF, repeated ischaemic incidents, and the likelihood of haemorrhage. This review consolidates GDF-15 biology, pathophysiology, diagnostic and prognostic applications, and therapeutic implications and offers a critical evaluation of existing evidence gaps and future research requirements.

Introduction

GDF-15: biology and pathophysiology

Molecular architecture and regulation

GDF-15 is a member of the TGF-β superfamily and is produced as a precursor protein that undergoes proteolytic cleavage to generate a 25 kDa disulphide-linked dimer.[1] Its transcription necessitates two p53-responsive promoter sites, hence associating its expression with oxidative stress, mitochondrial malfunction, and DNA damage pathways.[2] The placenta is the primary generator of GDF-15, with levels significantly increasing throughout pregnancy.

Pathophysiological mechanisms

Inflammation and immune regulation

GDF-15 exhibits a dual and context-dependent function in the regulation of inflammation. In the case of acute tissue injury, it demonstrates anti-inflammatory effects by diminishing leukocyte integrin activation and restricting neutrophil recruitment, therefore averting excessive inflammatory cell infiltration and subsequent tissue damage.[1,2] These systems are believed to facilitate the prompt containment of harm and sustain cellular homeostasis. In chronic atherosclerotic disease, GDF-15 seems to transition towards a pro-inflammatory phenotype. Experimental and human evidence indicates that a sustained increase of GDF-15 may perpetuate low-grade inflammation, alter macrophage phenotype, and facilitate the growth and instability of atherosclerotic plaques.[1] This bidirectional behaviour highlights GDF-15's intricate role in cardiovascular (CV) inflammation, acting as both a protective and detrimental modulator based on the temporal and clinical context.

Cellular origins in health and disease

In pathological situations, GDF-15 is synthesised by: Cardiomyocytes during ischaemia and post-myocardial in-

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farction remodelling.[3–5] Endothelial cells and vascular smooth muscle cells in atherosclerotic plaques.[1] Adipose tissue acts as an adipokine during metabolic stress.[4] Extracardiac organs in chronic heart failure (HF).[5] In acute myocardial infarction, cardiac output predominates, but chronic HF redirects output to peripheral tissues, including the liver, kidneys, and skeletal muscle.[5]

Endothelial dysfunction and accelerated vascular senescence

An increasing amount of epidemiological evidence indicates that GDF-15 is significantly correlated with indicators of vascular ageing and endothelial dysfunction. Community-based cohort studies indicate that elevated circulating GDF-15 levels are associated with enhanced arterial stiffness, compromised endothelial nitric oxide-mediated vasodilation, and early structural vascular abnormalities. These associations endure following the adjustment for conventional CV risk variables, indicating that GDF-15 may signify early microvascular damage and endothelial ageing. Given that endothelial dysfunction precedes numerous CV disorders, GDF-15 may serve as a sentinel biomarker for vascular health, detecting subclinical alterations that occur prior to the manifestation of overt disease.[6–10]

Diagnostic and prognostic functions of disease category

Community-based populations

Extensive cohorts, such as Rancho Bernardo and Framingham, indicate that GDF-15 serves as a predictor:

- overall mortality,
- CV mortality,
- mortality associated with cancer,
- even subsequent to the adjustment for traditional biomarkers such as NT-proBNP, hs-troponin, and hs-CRP.[7–9]

Lifestyle variables, such as suboptimal CV health indicators and tobacco use, correlate with elevated GDF-15 levels.[11,12]

Oxidative and metabolic strain

GDF-15 is acutely responsive to oxidative and metabolic stress, serving as a circulating biomarker indicative of systemic physiological burden. Increased GDF-15 levels are strongly associated with heightened oxidative stress marker expression and metabolic dysregulation, signifying an augmented state of cellular damage and stress signalling. These correlations are routinely noted in illnesses such as chronic renal disease, diabetes, and obesity, where prolonged metabolic stress fosters chronic inflammation and mitochondrial impairment. GDF-15 functions as a sensitive marker of disrupted metabolic homeostasis, amalgamating signals from oxidative processes, inflammation, and organ stress into a singular measurable biomarker. This renders it especially beneficial for detecting persons predisposed to cardiometabolic decline prior to the onset of clinical symptoms.[12]

Myocardial remodelling

In chronic HF, GDF-15 is persistently increased and significantly correlated with detrimental myocardial remodelling. Elevated GDF-15 levels are associated with augmented myocardial fibrosis, compromised left ventricular (LV) systolic and diastolic function, and enhanced neurohormonal activation.[5] These alterations illustrate the interaction among mechanical stress, inflammation, oxidative injury, and cellular apoptosis that contribute to advancing cardiac injury. GDF-15 thereby consolidates many upstream damage pathways into a prognostic indicator that accurately reflects the extent of structural and functional heart decline. Consequently, it is widely acknowledged as a crucial biomarker of pathological remodelling and disease progression in chronic HF.

Coronary artery disease (CAD)

In patients with CAD, GDF-15 is independently correlated with: multivessel CAD, diabetes and renal impairment systemic inflammation

In the Heart and Soul Study, GDF-15 was a predictor of CV mortality, HF hospitalisations, and recurrent ischaemic episodes in stable CAD.

Acute coronary syndromes (ACS)

In FRISC-II, PLATO, and PROVE-IT TIMI-22:
GDF-15 surpasses hs-CRP, NT-proBNP, and cardiac troponins in multivariable models.[13–20] GDF-15 is a robust predictor of both short- and long-term mortality. The risk increases incrementally throughout tertiles (1.5%, 5%, 14.1%).[16] Continued increase following acute coronary syndrome indicates persistent remodelling and risk of HF.[16,21] Patients with GDF-15 levels over 1200–1800 ng/L derive the most advantage from early invasive intervention.[19,20]

Heart failure

Chronic HFrEF/HFpEF
GDF-15 is associated with:
HF severity (NYHA classification, congestion), BNP/NT-proBNP, high-sensitivity cardiac troponin T, inflammation, cachexia, renal impairment.[21]

In HFpEF, increased GDF-15 indicates systemic inflammation associated with comorbidities such as diabetes and hypertension (HT).[22]

Acute HF
In advanced heart failure necessitating mechanical circulatory support, GDF-15 levels decrease swiftly after LV assist device (LVAD) implantation, indicating early restoration of peripheral organ function rather than direct cardiac unloading—an effect not observed in natriuretic peptide levels like BNP.[23] GDF-15 serves as a significant prognostic marker in cardiogenic shock, with elevated levels predicting short-term mortality and reflecting the extent of systemic stress and multi-organ involvement.[24] The RELAX-AHF trial demonstrated that decreases in circulating GDF-15 during serelaxin therapy were significantly correlated with enhanced clinical outcomes, highlighting its efficacy as a dynamic biomarker for treatment response in acute heart failure.[25] These observations collectively underscore GDF-15 as a sensitive biomarker along the

continuum of acute and severe heart failure, including haemodynamic impairment, systemic inflammation, and organ dysfunction, into a singular prognostic indicator.

Pulmonary vascular and right-heart pathology

GDF-15 improves risk stratification in several right-heart and pulmonary vascular conditions. In acute pulmonary embolism, increasing GDF-15 levels indicate individuals at increased risk for negative outcomes, offering additional predictive value beyond clinical evaluation alone.[26] In pulmonary arterial hypertension, GDF-15 is associated with disease severity and right-ventricular strain, perhaps surpassing natriuretic peptides in specific prediction models.[26,27] These relationships highlight its efficacy as a biomarker that encompasses cardiopulmonary stress, right-ventricular dysfunction, and systemic inflammatory activation.

Clinical applications and therapeutic consequences

Risk stratification and triage

Elevated GDF-15 levels identify patients with acute coronary syndrome who either derive greater advantages from early revascularisation or necessitate more rigorous antithrombotic treatment.[19, 20] In chronic HF, GDF-15 facilitates risk assessment and helps identify patients susceptible to unfavourable remodelling.

Prediction of bleeding risk

GDF-15 is a crucial element of bleeding-risk models established from the ARISTOTLE and RE-LY trials, exhibiting substantial predictive capability for major non-CABG-related haemorrhage and markedly enhancing risk classification beyond high-sensitivity cardiac troponins and conventional clinical variables. Increased GDF-15 levels predict bleeding problems in patients with ACS on dual antiplatelet therapy, hence identifying those at increased haemorrhagic risk during rigorous antithrombotic treatment.[28]

Assessment of treatment efficacy

Valsartan reduces BNP levels but does not affect GDF-15 (Val-HeFT), indicating distinct molecular processes.[21] Serelaxin induces swift decreases in GDF-15 during acute HF (RELAX-AHF).[25] Empagliflozin elevates GDF-15, signifying regulation of metabolic stress.[29]

Potential for therapeutic targeting

GDF-15 modulates appetite regulation and systemic metabolic management via the GFRAL–RET signalling pathway, indicating possible therapeutic implications in various interrelated domains. GDF-15's regulation of energy balance identifies it as a potential target for obesity and metabolic syndrome therapy. Furthermore, its pivotal position at the intersection of inflammation, metabolic stress, and cardiac dysfunction underscores the promise for therapeutic strategies targeting GDF-15 pathways to enhance outcomes in cardiometabolic disorders and HF.[30]

Cardiac arrhythmias

Individuals with lone atrial fibrillation (AF) or paroxysmal AF (PAF) frequently have elevated circulating GDF-15 levels, indicating increased atrial stress and systemic inflammation. These rises are associated with age, atrial dimensions, and structural atrial remodelling, indicating that GDF-15 may function as a sensitive measure of atrial substrate susceptibility. Besides basic atrial arrhythmias, GDF-15 has emerged as a prognostic indicator in non-ischaemic cardiomyopathy, with increased levels predicting severe arrhythmic events, including prolonged ventricular arrhythmias and the need for implantable cardioverter-defibrillator interventions. These data collectively demonstrate the promise of GDF-15 as a comprehensive biomarker connecting atrial disease, cardiac stress, and the risk of malignant arrhythmias (**Tables 1, 2**).[30,31]

Cardiometabolic and systemic disorders

Elevated levels are observed in individuals with metabolic syndrome, type 2 diabetes, non-alcoholic fatty liver disease (NAFLD), and obesity, indicating underlying metabolic stress and inflammation.[30] Environmental and toxic exposures, including cadmium, correlate with substantial elevations in GDF-15, underscoring its responsiveness to oxidative and metabolic damage mechanisms.[32,33] GDF-15 is persistently increased in many cardiometabolic and systemic diseases. Increased circulating concentrations are correlated with the severity of diabetic foot ulcers, suggesting a potential role in wound-healing assessment and risk stratification.[34] Ultimately, it functions as a growth biomarker in congenital heart disease, especially in younger children when conventional dietary indicators are less dependable.[35] Moreover, GDF-15 functions as an autonomous predictor of coronary plaque burden in individuals with HIV, signifying its robust association with chronic inflammation and vascular injury.[36,37]

Constraints and prospective directions

Constraints

Primary limitations

The primary limitations of the existing evidence encompass the utilisation of different immunoassays and poor calibration across analytical platforms,[3] leading to heterogeneity in reported GDF-15 values. Threshold values vary significantly among research, restricting comparability and obstructing the formulation of standardised clinical cut-offs. Furthermore, the majority of accessible data originate from observational cohorts, which limits causal inference and heightens vulnerability to residual confounding.[7,16] Renal impairment, advanced age, and multimorbidity significantly affect circulating GDF-15 levels, confounding the interpretation and risk assessment across various individuals.[7,12] Ultimately, mechanistic pathways are inadequately comprehended in human studies, underscoring the necessity for more profound translational research to elucidate GDF-15's biological function in CV disease (CVD).

Table 1 – The main topic points of recent studies

Reference no.	Authors	Subjects	Main theme
Ref [30]	Dallmeier et al.	Patients with stable coronary heart disease	Baseline GDF-15 independently predicts CVE and 10-year total mortality. Despite adjusting for well-established cardiovascular risk variables and cardiac biomarkers, 12-month relative changes were associated with subsequent CVE and total mortality.
Ref [32]	Hagström et al.	Patients with acute coronary syndromes	Higher GDF-15 levels in ACS patients increase the risk of all kinds of severe non-CABG-related bleeding, spontaneous MI, stroke, CV and total mortality, and seem to improve risk stratification for CV-mortality and major bleeding beyond known risk factors.
Ref [34]	Schopfer et al.	Patients with stable ischemic heart disease	Higher GDF-15 levels predict major CV events in stable ischemic heart disease. Other risk factors may not explain GDF-15 risk.
Ref [35]	Fuernau et al.	Acute myocardial infarction patients	GDF-15 on admission independently predicts short-term mortality in infarct-related cardiogenic shock.
Ref [39]	Wallentin et al.	Patients with non-ST-elevation acute coronary syndrome	Lifetime perspective suggests early invasive therapy for most non-ST-elevation acute coronary syndrome patients.
Ref [42]	Chan et al.	Patients with heart failure	Inflammatory damage (GDF15) may be relevant in both HF syndromes beyond haemodynamic stress (NT-proBNP).
Ref [46]	Cotter et al.	Patients with heart failure	GDF-15 elevations, but not baseline amounts, were associated with worse RELAX-AHF outcomes. Serelaxin reduced GDF-15 more than placebo.
Ref [47]	Wollert et al.	Community-dwelling individuals	GDF-15 shows CV disease development, progression, and prognosis that clinical risk factors and other biomarkers cannot.
Ref [48]	Abu-Assi et al.	Patientss with acute coronary syndromes	An update on clinically utilised ACS bleeding risk ratings.
Ref [49]	Wallentin et al.	Patients with atrial fibrillation	GDF-15 causes atrial fibrillation-related haemorrhage, mortality, and stroke. N-terminal pro-brain natriuretic peptide and high-sensitivity troponin I did not influence bleeding or death.
Ref [50]	Hijazi et al.	Patients with atrial fibrillation	ABC-bleeding beat HAS-BLED and ORBIT scores and may assist atrial fibrillation patients choose anticoagulation.
Ref [51]	Kato et al.	Individual patient meta-analysis	GDF15 predicts ASCVD CV mortality and HHF. GDF-15 improves MI and stroke prognosis, but not ACS.
Ref [52]	Omar et al.	Patients with heart failure	Empagliflozin increased plasma GDF-15 in HFrEF patients without raising hsTNT or hsCRP
Ref [53]	Xiao et al.	Review	GDF-15-mediated energy control may treat glucolipid metabolic disorders (GLMD). GDF-15 increases appetite in patients with diabetes, obesity, non-alcoholic fatty liver disease (NAFLD), and other disorders. GDF-15's role in GLMD's pathophysiology may lead to a novel therapy

Knowledge deficiencies

Significant gaps persist in the existing comprehension of GDF-15, necessitating elucidation through forthcoming study. Inadequate characterisation of the longitudinal trajectories of circulating GDF-15 across various phases of cardiovascular and metabolic illnesses constrains its effectiveness for dynamic risk evaluation. Secondly, the absence of defined disease-specific reference ranges complicates the identification of clinically significant cut-off values for various illnesses. The molecular role of GDF-15 in critical disease processes—such as myocardial inflammation and fibrosis in HFpEF, atrial remodelling in AF, and vascular remodelling in pulmonary HT—remains little defined. The genetic regulation of GDF-15 expression, particularly the impact of single nucleotide polymorphisms, necessitates further examination to elucidate interindividual variability and heritable factors influencing circulating levels.[9]

Anticipated pathways

Future research must prioritise several critical domains to enhance the clinical and translational application of GDF-15. First, the development and universal adoption of standardised immunoassay platforms is essential to minimise inter-laboratory variability and enable reliable comparisons of results across studies. Secondly, incorporating GDF-15 into multi-omics frameworks—such as genomics, proteomics, metabolomics, and transcriptomics—could elucidate fundamental biological pathways and improve disease phenotyping. Third, clinical decision-support technologies based on machine learning that integrate GDF-15 could enhance personalised risk assessment and treatment stratification. Fourth, prospective clinical trials are necessary to assess GDF-15–guided management options and to ascertain its supplementary value in standard cardiovascular therapy. A thorough examination

Table 2 – The main topic points of recent studies

Reference no.	Authors	Subjects	Main theme
Ref [54]	Li et al.	Patients with "lone" atrial fibrillation	In AF of unknown aetiology (UeAF), plasma GDF-15 was higher than sinus rhythm and lower than paroxysmal AF (PAF). Left atrial diameter and age substantially influence GDF-15.
Ref [55]	Chen et al.	Patients with atrial fibrillation	In this community-based biracial group, greater GDF-15 concentrations independently predicted incident AF.
Ref [56]	Carballo-Casla et al.	Older adults	The metabolic syndrome raised elderly GDF-15 levels. Abdominal obesity, hyperglycemia, low HDL-cholesterol, and inflammation caused this link.
Ref [57]	García-Esquinas et al.	Non-smoking older adults	Cd exposure raises CVD risk. CD may boost GDF-15.
Ref [58]	Zang et al.	Ischemic Stroke patients	GDF-15 levels independently predicted poststroke depression (PSD) in acute ischemic stroke, suggesting it may be a PSD biomarker.
Ref [59]	Sendur et al.	Patients with diabetic foot ulcer	Diabetic foot ulcer patients have elevated GDF-15. Advanced lesions are more common. GDF-15 measurement may help treat diabetic foot ulcers.
Ref [60]	Paneitz et al.	Children with Congenital Heart Disease	GDF-15 is an important growth indicator in congenital cardiac disease (CHD) children, especially those under 2 with HF. Prealbumin has no long-term growth biomarker.
Ref [61]	May et al.	Patients with nonischemic dilated cardiomyopathy	Serum GDF-15 independently predicted major arrhythmic episodes and mortality in nonischemic HF patients on optimal medication treatment. This biomarker may stratify sudden death risk in this population.
Ref [62]	Asrih et al.	Patients with metabolic syndrome	Preclinical animal studies show that GDF15 mimics lower food intake and weight. Thus, GDF15 might fight global obesity.
Ref [63]	Tridamayanti et al.	Acute myocardial Infarction Patients	At 3 months, MI patients with elevated GDF-15 risked major cardiac adverse events (MACE).
Ref [64]	Royston et al.	People living with and without HIV	GDF-15 and smoking synergistically increase coronary plaque volume in people living with HIV (PLWH). GDF-15 levels independently predicted coronary artery plaques in HIV-negative individuals.
Ref [65]	Deng et al.	Patients With Chronic Obstructive Pulmonary Disease	Chronic obstructive pulmonary disease (COPD) patients may readily assess sarcopenia using serum GDF15 levels.
Ref [66]	Mei et al.	Patients with type 2 diabetes mellitus	CAD and diabetic patients exhibited differing GDF-15 and ApoB/ApoA1 levels. Diabetics may predict CAD using ApoB/ApoA1 and GDF-15.
Ref [67]	Duceppe et al.	Patients 45 years or older having major noncardiac surgery	GDF-15 accurately predicts 30-day major cardiovascular events and cardiac risk in noncardiac surgery patients.

of GFRAL–RET signalling and its regulatory mechanisms in cardiovascular pathology may provide potential treatment avenues.

Conclusion

GDF-15 is a reliable biomarker indicative of cardiometabolic stress, inflammation, vascular dysfunction, and detrimental remodelling. In specific cardiovascular contexts, elevated GDF-15 consistently predicts mortality, recurrent ischaemic events, the advancement of HF, and the risk of haemorrhage. Despite its established diagnostic and prognostic significance, considerable limitations—such as assay variability, insufficient mechanistic understanding, and a lack of standardised thresholds—hinder its practical application. Future mechanistic and interventional studies will ascertain whether GDF-15 may transition from a prognostic marker to a therapeutic target.

Conflict of interest
The author(s) declare(s) that there is no conflict of interest regarding the publication of this paper.

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