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Growth differentiation factor-15 in heart failure: new update of clinical relevance

Alexander E. Berezin[1], Viacheslav Poliasnyi[2], LudmilaA Kovalevskaya[3], Alexander A. Berezin[4]

[1]Therapeutic Unit, Internal Medicine Department, Zaporozhye State Medical University, Zaporozhye, Ukraine

[2]Department of Public Health, Chief Physician of the Regional Oncological Dispensary, Odessa Medical Institute of the International Humanitarian University, Odessa, Ukraine

[3]Internal Medicine Department Vice-Rector for scientific and medical work, Odessa Medical Institute of the International Humanitarian University, Odessa, Ukraine

[4]Internal Medicine Department, Medical Academy of Postgraduate Education, Zaporozhye, Ukraine

Abstract— Heart failure (HF) remains a leading cause of mortality in patients with overt cardiovascular disease (CVD). New Universal Definition and Classification of HF is supposed to use biomarker strategy based on measure of circulating (mainly natriuretic peptides and high-sensitive cardiac troponins) and genetic indicators to identify patients at higher risk of HFand choose optimal strategy to diagnose and treat. Although the first-generation biomarkers (natriuretic peptides, high sensitive cardiac troponins) are widely used, the second-generation biomarkers of fibrosis and inflammation may have additional promising benefit in clear assessment of adverse cardiac remodeling and providing differentiation between several subtypes of HF. Growth differential factor-15 (GDF15) is a stress-induced multifactorial cytokine, which belong to the transforming growth factor beta superfamily. GDF15is markedly expressed in various cells and involved in glucose and energy homoeostasis, regulation of appetite, and body weight loss. GDF15 influences tissue protection from ischemia / reperfusion, and oxidative stress damage. The aim of the narrative review is to elucidate the diagnostic and therapeutic role of GDF15 in HF. We found that GDF-15 is a promising indicator of poor clinical outcomes and predictor of HF, and it could be a powerful component of a multiple biomarker strategy in managing HF patients.

Keywords— Heart failure; biomarkers; growth differential factor-15; prediction; outcomes

1. Introduction

Heart failure (HF) remains a global medical and social problem due to a rising economic burden and non-optimal declining a risk of mortality of HF-related complications worldwide despite an impressive progress in its diagnosis, treatment and prevention [1]. Numerous research efforts concentrate on establishing timely diagnosis, improving prognosis and treatment of the disease with the aim of attenuating a risk prediction and developing personifying therapeutic approaches [2-4]. In this context, non-invasive highly accurate determination of suspected HF and overt HF with circulating biomarker models is becoming remarkably important for routine clinical practice [5, 6].

New Universal Definition and Classification of HF is supposed to use biomarker strategy based on measure of circulating (mainly natriuretic peptides and high-sensitive cardiac troponins) and genetic indicators to identify patients at higher risk of HF (stage A) and pre-HF (stage B), and choose the optimal strategy to diagnose and treat HF [6]. Current clinical guidelines of 2017 American College of Cardiology (ACC)/American Heart Association (AHA)/ Heart Failure Society of America (HFSA) and 2021 European Cardiology Society (ESC) are quite distinguished in the spectrum of biomarkers recommended and also in a way to manage them among patients with HF with reduced (HFrEF), mildly reduced (HFmrEF) and

preserved (HFpEF) ejection fraction [6, 7]. In fact, 2017 ACC/AHA/HFSA clinical guideline of HF recommends to use natriuretic peptides (NPs) to diagnose, predict, manage and stratify patients with HFrEF / HFpEF, whereas biomarkers of myocardial injury (cardiac troponins), and next-generation biomarkers of fibrosis and inflammation (soluble suppressor tumorigenisity-2 [sST2], galectin-3) have been predominantly implemented to stratify HFpEF patients at risk and improve both diagnostic and predictive abilities of NPs for these individuals. In contrast, both 2016 ESC guideline for HF and its 2021version do not support an idea to use next-generation biomarkers whatsoever [6]. However, there is a strong consent between a wide range of investigators in understanding that conventional biomarker models based on NPs would not show a strict resemblance in their predictive ability for HFrEF and HFpEF [8-10]. Indeed, biomarkers of biomechanical stress (NPs), myocardial injury (cardiac troponins) appeared to be by far superior in prediction of HFrEF than HFpEF, whereas biomarkers of oxidative stress, inflammation and fibrosis (growth differentiation factor -15 [GDF15], sST2, galectin-3), and adipose tissue dysfunction are best fitted to the prediction and risk stratification of HFpEF [11, 12]. Therefore, the second-generation biomarkers of fibrosis and inflammation may have additional promising benefit in clear assessment of adverse cardiac remodeling and providing differentiation between several subtypes of HF [13]. The aim of the narrative review is to elucidate the diagnostic and therapeutic role of GDF15 in HF.

2. Methods and Methodology

The bibliographic database of life science and biomedical information MEDLINE, EMBASE, Medline (PubMed), the Web of Science, and the Cochrane Central were searched for English publications satisfying the key words of this study. We used the following key words [heart failure]; [HFrEF]; [HFmrEF]; [HFpEF]; [growth differential factor-15]; [cardiovascular risk], [cardiovascular risk factors], [cardiac biomarkers]; [circulating biomarkers]; [diagnosis]; [prognosis]. All authors independently selected articles, evaluated the quality of the data, presentation, and interpretation correspondence to the main idea of the study, and constructed the final list of the references

3.Growth differential factor-15: biological role and function in several conditions

Growth differential factor-15 (GDF15) is a stress-induced multifactorial cytokine, which belong to the transforming growth factor beta superfamily [14]. It is markedly expressed in a wide range of cells in both normal and pathological conditions, while it released in the abundant as a released from the cells in result of tissue injury due to oxidative / nitrosative stress, ischemia / necrosis, reperfusion, and inflammation [15, 16]. In addition, the induction of GDF15 synthesis was found to be independent of protein synthesis, a hallmark of immediate-early gene regulation [17]. Therefore, the effects of GDF15 relate closely to type of tissue and appear to be controversial (Figure 1).

Acting as suppressor of JNK, Bcl-2-associated death promoter (Bad), ALK (activing-A receptor kinase) -1,2,3,4,5 and 6 types, and epidermal growth factor receptor (EGFR) and activator of Smad / eNOS, PI3K /AKT signaling pathways GDF-15 improves glucose and energy homoeostasis, potentiates weight loss and interferes tissue protection from ischemia / oxidative stress damage [18, 19]. GDF15 is able to binds with high affinity specific receptors called GDNF family receptor α–like (GFRAL) that being a member of the glial-derived neurotropic factor receptor α family are widely expressed in the area postrema and regulates appetite and food behavior [20]. In fact, previous data suggested that GDF15 was an early mediator of the injury response in several tissues, including myocardium, kidney, liver, vasculature, endothelium, and lung, which might dually regulate apoptosis, inflammation, cell survival, and proliferation, in these injured organs disease processes [21].

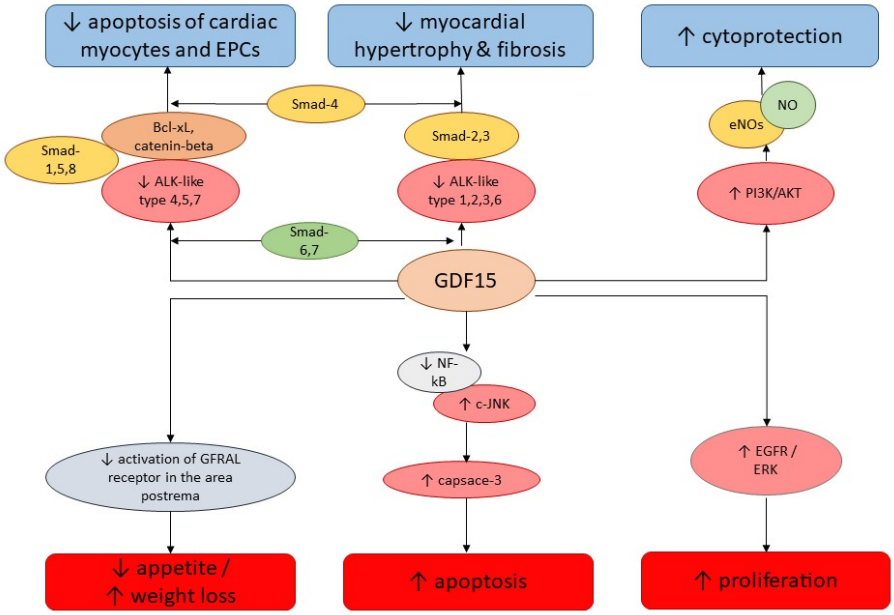

Figure 1: Tissue specific effects of GDF15
Abbreviations: ALK, activing-A receptor kinase; GDF15, growth differential factor-15 (; PI3K, phosphoinositol-3-kinase; ERK, extracellular signal-regulated kinase); EPCs, endothelial progenitor cells; EGFR, epidermal growth factor receptor; c-JNK, c-Jun N-terminal kinase; NF-kB, nuclear factor kappa beta; NO, nitric oxide; eNOs, endothelial NO synthase

Consequently, GDF15 is considered as an adaptive mediator supporting tissue protection, but not primary damage factor, while its pro-apoptotic and proliferative abilities were established in several investigations [22, 23]. For instance, elevated levels of GDF15 was determined in humans who have been treating with metformin in strong association with the weight loss and fasting glucose improvement [24]. On the other hand, GDF15 via alternative signal way that is mediated by GFRAL has demonstrated a powerful regulating impact on glucose and free fatty acid homeostasis [25]. In additional, GDF15 was identified as a factor that was able to suppress hepcidin and thereby induce ineffective erythropoiesis and occurrence of anemia in HF individuals [26]. Probably, GDF15 is involved in the iron metabolism, while there was not received a strong evidence regarding ferritin synthesis in connection with GDF15 concentrations [26].

4.Growth differential factor-15 in patients at higher CV risk

Clinical relevance GDF-15 in energy homeostasis was thoroughly established in the XENDOS (XENical in the prevention of Diabetes in Obese subjects) trial that included 496 obese nondiabetic individuals at high CV risk [27]. Investigators have found that the GDF15 levels were strongly associated with body mass index, waist-to-hip ratio, and insulin resistance [27]. Echouffo-Tcheugui JB et al. (2021) [28] also established that higher circulating levels of GDF15 were positively associated with (highest vs. lowest quartile) occurrence of T2DM, HF, atherosclerotic CV events, elevated levels of hs-cTnT and N-terminal pro natriuretic peptide (NT-proBNP) in general population. However, GDF15 was found to be crucial mediator of anorexia-cachexia syndrome in advanced stages of HF, diabetes mellitus, nonalcoholic fatty liver disease, chronic renal disease, and cancer [29-31].
Collectively, elevated levels of GDF15 were remarkably associated with increased risks of CVD, chronic kidney disease, and cancer regardless of conventional CV risk factors [32]. The patients with end-stage of

chronic kidney disease (CKD) enrolled in the C-PROBE (Clinical Phenotyping and Resource Biobank) study and the SKS (Seattle Kidney Study) had high circulating levels of GDF15 that were strongly correlated with intrarenal expression of the marker and significantly associated with elevated risk of CKD progression [33]. Among 1391 older adults with no history of CVD, who were enrolled in the Rancho Bernardo Study, there were no found significant associations between circulating GDF15 and other biomarkers, such as C-reactive protein, NT-proBNP, and high sensitive cardiac troponins, but elevated levels of GDF-15 were a robust predictor of all-cause, CV, and non-CV mortality [34]. In addition, the discriminative potency of GDF for mortality in a general adult population without known CVD was superior when compared with NT-proBNP and high sensitive C-reactive protein. Moreover, GDF15 was the only biomarker that predicted non-CV death among these individuals [34]. The PREDICTOR study has revealed that elevated levels of GDF15 independently better predicted all-cause mortality than insulin-like growth factor-binding protein-7, amino-terminal pro-peptide of type I procollagen and high sensitive cardiac troponin in elderly general population with multiple co-morbidities and high prevalence of asymptomatic ischemia-induced cardiac dysfunction [35].

Wallentin L et al (2014) [36] reported that GDF-15 level > 1383 ng/L well predicted major bleeding, CV mortality, and stroke in patients with atrial fibrillation who were included in the ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) trial. Yet, the discriminative potency for major bleeding and CV death retained superior than NT-proBNP and high-sensitivity cardiac troponin I [36]. However, in this trial GDF15 being strongly related to major bleeding were not found as predictor for HF, stroke, systemic embolism or sudden death, whereas NT-proBNP and high-sensitivity cardiac troponin I had a powerful prognostic values for these events [37]. The results of the PLATO (The Platelet Inhibition and Patient Outcomes) trial, in which 18,624 patients with acute coronary syndrome were consequently enrolled, have demonstrated the strongest associations between the levels of GDF15 and vascular and non-vascular deaths, and death due to major bleeding [38]. Recently reported data received by Song L et al (2021) [39] confirmed that high circulating levels of GDF15 were related to incident intracerebral hemorrhage and subarachnoid hemorrhage.

In cohort of 3641 patients with established coronary artery disease (CAD) the levels of GDF-15 > 1800 ng/L were substantially associated with an increased risk of major adverse CV events (MACEs) and all-cause death beyond traditional CV risks factors [40]. Interestingly, among patients with acute coronary syndromes (ACS) GDF-15 levels >1800 ng/L were strongly associated with an increased prevalence of CV risk factors [41]. Moreover, GDF-15 levels >1800 ng/L were found to independent predictor for all-cause death (HR=4.09; 95% CI=1.57-10.71; p = 0.004), the composited MACE, the incidence of newly HF but not of recurrent myocardial infarction [41]. To note, previously reported the results of sub-analysis from the ICTUS (Invasive versus Conservative Treatment in Unstable coronary Syndromes) trial, which included cardiac troponin positive non-ST elevation-ACS patients, GDF15 levels >1800 ng/L have yielded an increased hazard ratio for CV death or spontaneous myocardial infarction along with marginal decrease in mortality [42].

There were attempts to use a measure of GDF15 levels to improve predictive ability of the GRACE (Global Registry of Acute Coronary Events) score. Indeed, Widera C et al. (2012) [43] reported that GDF-15 added incremental information to a model containing the GRACE score and NT-proBNP. In addition, GDF15 levels appeared to be strongest predictor for the risk of ACS among diabetics when compared with other classic biomarkers including high selective cardiac troponins, creatine kinase-total, and creatine kinase-MB [44]. The meta-analysis of eight clinical studies has shown a sufficient relation between the highest levels of GDF15 and mortality ($p < 0.00001$; relative risk [RR] = 6.08; 95 % CI = 4.79-7.71) and recurrent myocardial infarction ($p < 0.00001$; RR = 1.76; 95 % CI = 1.49-2.07) when compared with the lowest concentrations of one [45]. Finally, Wang Y et al (2019) [46] performed a meta-analysis of 13 studies (total n= 43,547) and found a rigorous association between the levels of GDF15 and CV mortality (p = 0.000, RR

= 6.75, 95% CI = 5.81-7.84) and recurrent myocardial infarction (p = 0.000, RR = 1.95, 95% CI = 1.72-2.21). Thus, mutual anti-inflammatory, metabolic and tissue protective capabilities of GDF15 might shed light on its role in HF development [47].

5.Clinical relevance of growth differential factor-15 in HF

Increased levels of GDF were previously found in the majority of the adults and children with HFpEF and HFrEF in close relation with comorbidity burden, and echocardiographic indicators [48-51]. Most investigators reported that the levels of GDF15 demonstrated a strict similarity in HFpEF and HFrEF, whereas circulating levels of the first generation biomarkers, such as NT-proBNP and high sensitive cardiac troponins, were significantly lower in HFpEF than HFrEF [52, 53]. Importantly, GDF15 along with carnitine palmitoyltransferase IB-protein and oral anticoagulation therapy were independent predictors for weak muscle endurance after adjusting for age in patients with HFrEF and HFpEF [49].

However, there is a marginal mismatch between circulating levels of the biomarkers and its tissue expression that might influence adverse cardiac remodeling and tissue protection in HF. Indeed, adverse cardiac remodeling and systolic / diastolic dysfunction in HF were profoundly related to cardiac expressions of GDF15, but not its serum levels [50]. In contrast, elevated circulating levels of GDF15 were strongly associated with increased white adipose tissue expression and not with cardiac remodeling and function [50]. Yet, after myocardial infarctionthe cardiac expression of GDF15 has exhibited a tendency to dramatic increase, while the circulating levels remain respectively stable for some period until occurrence of cardiac dysfunction. Consequently, at the early stage of HF dynamic changes in cardiac expression of GDF15 appear to be more specific for adverse cardiac remodeling than elevated plasma levels of the biomarker. Another study, the results of which were reported by Rubiś P et al (2021) [51], confirmed the fact regarding a weak correlation between higher plasma levels of GDF15 and cardiac fibrosis determined with cardiac magnetic resonance assessment with late gadolinium enhancement among patients with non-ischemia-induced HF. Moreover, this biomarker did not allowed distinguishing dilated cardiomyopathy patients with HFrEF with and without replacement fibrosis. Notwithstanding these findings, there is strong evidence regarding a tight interrelation between circulating GDF15 and GDF15 mRNA expression levels in circulating mononuclear cells in HFrEF patients [51]. However, plasma GDF15 was found to be more sensitive for predicting NYHA class IV HFrEF, whereas GDF15 mRNA level in circulating mononuclear cells better predicted NYHA class II HFrEF than NYHA class IV [54].

Sarkar S et al (2020) [55] found that obese patients at high risk of HF and undergoing open-heart surgery with GDF15 >1,580 ng/L had the worst 2-year survival when compared to the patients with lower GDF15 levels. Among HFpEF patients included in the multicenter PROMIS-HFpEF (Prevalence of Microvascular Dysfunction in Heart Failure With Preserved Ejection Fraction) study elevated GDF15 levels mediated the relationship between metabolic comorbidity and echocardiographic parameters, such as mitral E velocity, E/e' ratio, and tricuspid regurgitation velocity [56]. A pool analysis of both cohorts of patients who were enrolled in the PIVUS (Prospective Investigation of the Vasculature in Uppsala Seniors) study (n=901) and the ULSAM (Uppsala Longitudinal Study of Adult Men) study (n = 685) unveiled that elevated levels of GDF15 were better associated with worsened left ventricular systolic function, but not diastolic dysfunction [57].

There is a large number of evidence regarding the fact about strong correlations between GDF-15 levels and severity of coronary atherosclerosis and NYHA functional class in ischemia induced HF patients [58]. Fluschnik N et al (2018) [59] reported that among 3785 participants oh the DAN-MONICA (Danish-Multinational MONitoring of trends and determinants in Cardiovascular disease) cohort a trend to increasing GDF15 levels for 27 year follow-up period was positively related to death of CHD and HF. Authors of the study concluded that repeated measurements of circulating levels of GDF15 yielded a slight improvement in the prediction of clinical outcomes when compared to a single measurement of this

biomarker.

Kanagala P et al (2020) [60] reported that both focal and diffuse fibrosis of myocardium corresponded to increased GFD15 levels, while GDF15 and composite event (all-cause mortality and/or HF hospitalization) rates did not distinguish in HFrEF and HFpEF patients. However, there is a large body of evidence regarding a possibility of GDF15 to improve prognostic information in term of predominantly HFrEFbeing added to NYHA functional class, LVEF, and serum levels of NT-proBNP [61, 62]. Recently reported systematic review provided by Rabkin SW, Tang JKK (2021) [63] has shown that to distinguish HFpEF from HFrEF GDF15 along with other inflammatory biomarkers might be incorporated into conventional biomarker strategy. Yet, Bouabdallaoui N et al. (2018) [64] reported that GDF-15 was not significantly modified by ARNI sacubitril/valsartan among out-patients with HFrEF, while the baseline levels of this biomarker were strongly associated with all-cause mortality and CV outcomes. There is evidence regarding the possibilities to modify the serum levels of GDF15 during cardiorespiratory fitness in patients having HFrEF or HFpEF. The post hoc analysis of the data obtained from ambulatory cohorts of HFrEF patients enrolled in the IRONOUT study and HFpEF participants who were included in the RELAX trial has revealed that second generation biomarkers including GDF15 were not able to be changed during exercise, but NT-proBNP demonstrated steadily tendency to have decreased value [65]. Authors concluded that GDF15 possibly is not suitable a reliable surrogate biomarker for serial measures within exercise training among HFrEF/HFpEF patients due to a lack of consistent independent association with cardiorespiratory fitness regardless of conventional CV risk factors and the levels of NT-proBNP.

In the SERVE-HF (Treatment of Sleep-Disordered Breathing with Predominant Central Sleep Apnoea by Adaptive Servo Ventilation in Patients with Heart Failure) trial the clinical outcomes of 1325 patients with HFrEF and central sleep apnoea were determined [66]. The results of the study have shown that current clinical predictive model for all-cause death, which included male sex, systolic blood pressure < 120 mmHg, DM, loop diuretic, cardiac device, 6-min walking test distance, and NT-proBNP, can be significantly improved by adding GDF15.

Finally, GDF-15 is considered a promising indicator of poor clinical outcomes in HFrEF / HFpEF and predictor of occurrence of HFpEF rather than HFrEF, as well as a powerful component of a multiple biomarker strategy in managing HF patients [67].

6. Conclusion

GDF-15 is suggested to be a useful second-generation biomarker to detect prevalent HF and predict all-cause mortality in general population. Measures of GDF15 levels are suitable to reclassify patients with suspected or overt HFpEF and HFrEF at higher risk of MACEs, recurrent hospitalization, and HF-related fatal and non-fatal clinical outcomes. Among individuals with established HFrEF, HFmrEF, orHFpEF GDF15 being added to the conventionally used NPs allows refining prognostic assessment of the disease. Practical utility of continuous monitoring of GDF15 levels to manage HF with different phenotypes requires serious elucidation in large clinical trials in the future.

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