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Association between Growth Differentiation Factor 15 and Chronic Heart Failure

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***Abstract*— Background. Heart failure (HF) is a major health problem because it is common, and has a high rate of hospitalization and high rate of mortality. While substantial advances have been achieved in the treatment of heart failure over the past two decades, HF mortality remains as high as cancer mortality. Aim of the study To investigate the association between serum GDF-15 and chronic HF, and its potential usefulness as a biomarker in these patients. Patients and methods This study was conducted on a total of seventy nine patients at Fayoum University hospitals and was classified as : Fifty patients having the typical symptoms and signs of heart failure and diagnosed with either heart failure with reduced ejection fraction (HFrEF) or heart failure with preserved ejection fraction (HFpEF). Twenty nine patients as control group. Blood samples for GDF-15 level were analyzed. The results demonstrated significant relation between elevated GDF-15 levels and HF patients in comparison to patients with no HF in the control group.. Conclusion: Our results suggest that GDF15 could be an independent marker for diagnosis, and management of patients with chronic heart failure.**

***Index Terms*— GDF-15 , chronic HF, biomarker, HFrEF, HFpEF.**

I. Introduction

Despite the substantial advances in the cardiovascular medicine and surgery field in the past half century HF remains a stubborn major problem and is now considered as the greatest challenge in the cardiovascular medicine (1). Irrespective of the type of HF, either systolic or diastolic, coronary artery disease (CAD) has supplanted hypertension as the most prevalent cause for congestive heart failure, with a high rate of mortality and future hospitalizations. (2.3) Heart failure (HF) is a heterogeneous syndrome resulting from a diverse array of adverse stimuli, acting singly or in concert to impair ventricular function. This, in turn, is responsible for a variety of clinical manifestations, including shortened survival. An important goal of cardiologists and cardiovascular scientists has, for more than a century, been to dissect and disentangle the various etiological and pathophysiological mechanisms that are responsible for HF in order to assess prognosis and to provide optimal management.(4) Dysfunction of tissues and organs remote from the heart cannot, however, be explained solely by reduced perfusion and it is generally believed that other systemic processes (e.g. neurohumoral activation) are involved. In other words, the pathophysiology of heart failure is complex and incompletely understood and, consequently, so is the pathophysiological basis of treatment. It has even proved difficult to agree a simple definition of heart failure (5). Growth differentiation factor-15 (GDF-15), also known as GDF-15/MIC- 1(macrophage inhibitory cytokine-1), is a divergent member of the human transforming growth factor β (TGF-β) superfamily (6). GDF-15 expression increases in response to tissue repair after acute injury, macrophage activation, cancer, and inflammation (7.8). Increasing evidence suggests that GDF-15 is an integrative signal in pathology, with both adverse and beneficial effects, depending on the state of the cells and their microenvironment (9). GDF-15 role in the pathophysiology of heart failure is still not fully understood, GDF-15 are thought to be secreted in response to pathological stress such as ischemic insults and pressure overload causing cardiac myocytes hypertrophy. in a mouse model of myocyte enhance factor 2C (MEF2C)

Table (1) illustrates that there is statistically significant **high** mean of GDF-15

Variables	Mean GDF-15		p-value	Sig.
	Mean	SD		
Cases	**999.3**	605.4	**<0.001**	**HS**
Controls	143.5	114.6		

level with p-value <0.05 among cases of heart failure (999.3 ±603.4) versus (143.5± 114.6) among controls.

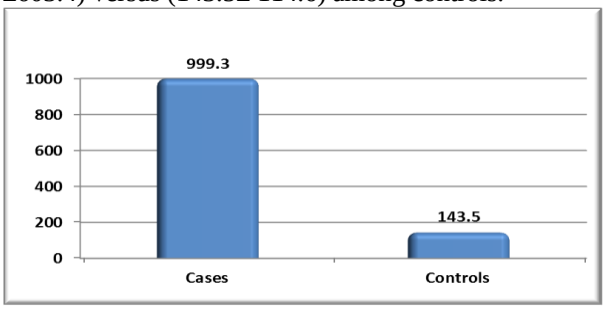

Figure (1): Mean GDF-15 in different study groups

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Table (2): Comparisons of growth differentiation factor 15 in different study sub groups.

Variables	Mean GDF-15		p-value	Sig.
	Mean	SD		
HFpEF	544.7	222.7	<0.001	HS
HFrEF	1386.5	556.9		
Controls	143.5	114.6		

Table (2) illustrates that there is statistically significant **high** mean of GDF-15
level with p-value <0.05 among cases of heart failure especially heart failure with
reduced ejection fraction (1386.5 ±556.9) followed by patients with preserved
ejection fraction heart failure with mean of (544.7 ±222.7) versus (143.5± 114.6) among controls

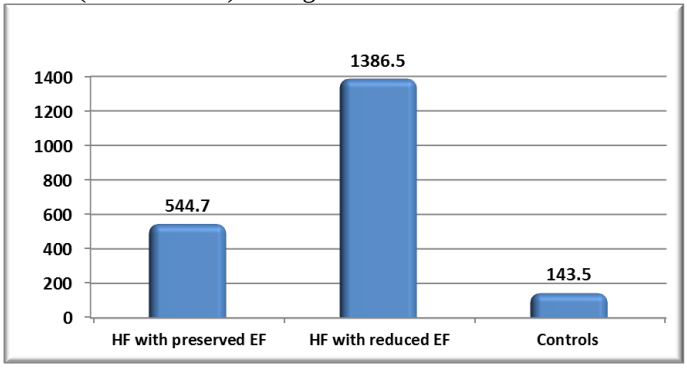

Figure (2): Mean GDF-15 in different study sub groups

II. DISCUSSION

The measurement of circulating biomarkers has become a cornerstone of HF management. Based on a wealth of clinical data demonstrating the diagnostic utility of natriuretic peptides in a variety of clinical settings, as well as sound knowledge of the physiological role of these peptides in HF, clinical practice guidelines now recommend the assessment of NT-proBNP or BNP to aid in the diagnosis of HF.**(12.13).** Experimentally, cardiac myocytes produce GDF-15 in response to mechanical stretch, ischemia, oxidative and nitrosative stress, and angiotensin II stimulation. **(11,14)**. Conceptually, these stimuli might also induce GDF-15 expression in the hypertrophied and failing human heart, and the circulating levels of GDF-15 may therefore reflect these processes. Our current findings offer further support for this recommendation. Recognizing that HF is essentially a clinical diagnosis, the presence of HF was confirmed in our patients by the presence of characteristic symptoms and signs, regardless of natriuretic peptide levels, thus allowing us to examine the diagnostic utility of GDF15 in a selected HF population with ischemic etiology. In our study we found that GDF15 levels were high among the HF cohort in comparison to the non HF control group . These findings are consistent with recent studies; (**Dalos, et al. 2019**) found that levels of GDF-15 constantly increase when left ventricular EF decreases in CHF patients in a study conducted over 249 patients. They found that levels of GDF-15 were 699 ± 554 pg/mL in the control cohort with a significant difference to the group with EF ≤ 30% (3173 ± 3008, $p < 0.001$) **(15)**. **Kempf, et al. 2007** studied circulating levels of GDF-15 were determined by immunoradiometric assay in 455 patients with CHF with a median left ventricular ejection fraction (LVEF) of 32% (interquartile range 25% to 39%).they found that 74.9% of the patients presented with GDF-15 levels >1,200 ng/l, the upper limit of normal in healthy elderly individuals **(16)**, **Anand , et al. 2010** had The circulating concentration of GDF-15 measured at baseline (n=1734) and at 12 months (n=1517) in patients randomized in the Valsartan Heart Failure Trial (Val-HeFT). They found GDF-15 levels at baseline ranged from 259 to 25 637 ng/L and were abnormally high (>1200 ng/L) in 85% of patients. The authors concluded that higher levels were associated with features of worse heart failure and biomarkers of neurohormonal activation, inflammation, myocyte injury, and renal dysfunction (17). **Wollert, et al. 2012** concluded that after an acute coronary syndrome, elevated levels of GDF-15 are indicative of an increased risk of developing adverse left ventricular remodeling and HF. In patients with established HF, the levels of GDF-15 and increases in GDF-15 over time are associated with adverse outcomes. The information provided by GDF-15 is independent of established risk factors and cardiac biomarkers, including BNP (18). **Zhu, et al. 2015** explored the association between plasma growth differentiation factor 15 (GDF-15) levels and chronic heart failure (CHF) in coronary heart disease patients. they found that plasma GDF-15 levels in coronary atherosclerosis patients with CHF [median 1622.48 (25-75th percentile: 887.53-1994.93) ng/L] were higher than those in coronary atherosclerosis patients without CHF [944.99 (856.12-999.78) ng/L] and control patients ($P < 0.05$) . the authors suggested that CHF patients have significantly increased GDF-15 levels compared to normal subjects, indicating that GDF-15 can be used as a biomarker for myocardial injury (19). Our study found that GDF 15 levels were also significantly elevated in patients with HFpEF. this was confirmed in the recent studies, **Santhankrishnan, et al. 2012** studied circulating levels of GDF15 in compensated patients with clinical HF with reduced ejection fraction (HFREF) (n = 51), HF with preserved ejection fraction (HFPEF) (n= 50), and community-based controls (n = 50). Compared with controls, patients with HFPEF and HFREF had higher median levels of GDF15 (540 pg/mL vs. 2529 and 2672 pg/mL, respectively) (20). **Stahrenberg, et al. 2010** selected A subgroup of patients from the DIAST-CHF observational trial, with a history of chronic heart failure (CHF) or positive Framingham criteria at presentation. They found that Growth differentiation factor 15 levels in HFpEF were significantly higher than in controls. GDF 15 correlated with multiple echocardiographic markers of diastolic function (21). **Dinh, et al. 2011** in a study that included 119 patients with normal ejection fraction and left ventricular diastolic dysfunction found that GDF-15 levels in HFpEF [median 1.08, interquartile range (0.88-1.30) ng/ml] were

significantly higher than in controls [0.60 (0.50-0.71) ng/ml, p = 0.003].Furthermore, GDF-15 was correlated with echocardiographic markers of diastolic dysfunction (22).. **Bonaca , et al 2011** measured GDF-15 in 3501 patients in PROVE IT-TIMI 22 study and found that patients at the highest quartiles of GDF-15 concentrations (>1800 ng/L) are at the highest risk of congestive heart failure suggesting that GDF-15 primarily reflects chronic disease burden in these patients. (23)

III. Limitations of the Study

Some limitations of our study should be noticed and hopefully taken into considerations in the future studies 1-The relatively small sample size of the study, therefore the results should be taken with caution. Larger studies in diverse populations are needed. 2-Due to financial constraints, investigating further relation of GDF-15 to other biomarkers as NT-proBNP to establish a solid evidence of the diagnostic significance of the GDF-15 in heart failure patients was lacking. 3-The non-randomized design of the study did not allow us to study the influence of drugs on the circulating levels of GDF-15. Before introducing GDF-15 into clinical practice, the influence of common medications of HF (e.g. diuretics, RAAS blockers, β blockers) on the circulating levels of this biomarker should be explored.

IV. Conclusion

In the light of our study we suggest that GDF-15 may play an important role in the future as an independent marker for diagnosis, and decision making regarding the management of a wide population of patients with heart failure in the upcoming era of growing importance of novel biomarkers.

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