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Exploring the Role of Glucagon-Like Peptide-1 in Heart Failure with Preserved Ejection Fraction among Patients with Type 2 Diabetes Mellitus

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ABSTRACT

Background: The prevalence of cardiac dysfunction in people with type 2 diabetes mellitus (DM) is as high as 35 %. Type 2 diabetes is associated with the development of heart failure with preserved ejection fraction (HFpEF) than with heart failure with reduced ejection fraction (HFrEF)**.** A considerable number of studies have pointed to the advantageous effects of Glucagon Like Peptide-1(GLP-1) on cardiovascular function. **Methods:** This case-control study was conducted on 48 subjects of them 16 subjects were healthy control (Group I), 16 subjects formed the type 2 DM without HF group (Group II), and 16 subjects formed the type 2 DM with HFpEF group (Group III). All patients underwent trans-thoracic echocardiography, routine laboratory tests and measurement of fasting levels of serum GLP-1 by (ELISA) kits. The study was conducted in Internal Medicine Department in collaboration with Cardiology Department and Clinical pathology Department, Faculty of Medicine, Zagazig University Hospitals **Results:** GLP-1 (pmol/L) level was lowest among diabetics with HFpEF followed by patients with diabetes without HF and the highest level was among the healthy controls. A statistically significant negative correlation between GLP-1 and H_2FPEF score has been detected among population with type 2 DM. In univariable logistic regression model to assess predictors of HFpEF among patients with type 2 DM, GLP-1 was the only predictor for HFpEF among diabetic patients **Conclusion:** Low levels of GLP-1 carry a potential risk for HFpEF development among patients with type 2 diabetes; this points to the causation relation between GLP-1 decline and HFpEF occurrence.

Introduction

The effect of incretin is defined as an increase in insulin secretion following oral glucose intake compared to insulin secretion following an isoglycemic IV glucose infusion. In healthy people, the incretin influence is accountable for up to 70% of insulin production after an oral glucose load **(1).** The incretin impact is attributed to effect of both

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glucose-dependent insulinotropic peptide (GIP) and glucagon-like peptide 1 (GLP-1) **(2).**

Although GLP-1 receptor agonist is well known for its insulinotropic and weight-lowering properties, it also has a number of beneficial effects on the cardiovascular system in rodents. These include increased cardiomyocyte survival by apoptosis suppression, improved regional and global cardiac output following damage and heart failure **(3)**, and amelioration of endothelial dysfunction **(4).**

Dr. Luchi and his colleagues identified heart failure with preserved ejection fraction (HFpEF) in 1982. They reported a group of patients with classic HF symptoms and preserved (≥ 50%) left ventricular ejection fraction (LVEF). **(5).** Nowadays, The European Society of Cardiology (ESC) defines HFpEF as maintained left ventricular EF (LVEF ≥ 50%) with diastolic dysfunction or structural heart disease, together with classic HF signs and symptoms and increased natriuretic peptide levels. **(6).**

Diabetes Mellitus (DM) is a significant risk factor for a variety of cardiovascular complications, including heart failure (HF) **(7)**. DM increases the likelihood of new-onset HF regardless of other established risk factors. Each 1% increase in glycated hemoglobin (HbA1c) is related to an 8% increase in the likelihood of HF in type 2 diabetes **(8)**.

In early clinical trials, GLP-1 was shown to improve LV contractile function in patients with chronic HF. A study on a small sample of type 2 DM patients with chronic HF demonstrated that short-term GLP-1 infusion for three days improved both systolic and diastolic function, however, these changes were not statistically significant **(9).**

Thus, in the current study, we aimed to assess the relation of GLP-1 with HFpEF development among patients with type 2 DM mellitus.

Methods

Study Design This case-control study was carried out in the Internal Medicine Department, Cardiology Department, and Clinical Pathology Department, Faculty of Medicine, Zagazig University Hospitals, within the period from December 2020 to December 2022. ***Patient Selection*** The study included 48 subjects of both sexes. The enrolled subjects were divided into three groups. Group I (Control group) enclosed 16 normal individuals, 12 (75%) males and four (25%) females, their ages ranged from 32-80 years with a mean and standard deviation of 51.3 ± 15.34 years. Group II (Diabetic without heart failure group) included 16 patients with type 2 diabetes without heart failure, nine (56.2%) males and seven (43.7%) females, their ages ranged from 43-74 years with mean and standard deviation of 62.06 ± 8.33 years. Group III (Diabetic with HFpEF group) involved 16 patients with type 2 diabetes of five years duration or more, with HFpEF, six (37.5%) males and 10 (62.5%) females, their ages ranged from 47-80 years with mean and standard deviation of 64.8 ± 9.92 years. Patients with diabetes (groups II and III) had been diagnosed as type 2 DM of five years duration or more (based on criteria of diagnosis of diabetes by the American Diabetes Association, 2014) **(10).** In our previous study **(11)**, we investigated the role of fasting serum glucagon as a potential marker for heart failure with preserved ejection fraction evolution among patients with type 2 diabetes mellitus. This study focused on assessing glucagon levels and their predictive value in distinguishing T2DM patients with and without HFpEF, demonstrating a significant correlation between elevated glucagon levels and the presence of HFpEF. However, in the current study, we aim to explore a different pathophysiological pathway by assessing the role of glucagon-like peptide-1 (GLP-1) in the development and progression of HFpEF in diabetic patients. While the preceding study had a smaller cohort with only 32 patients included in the study, 16 with T2DM and 16 with T2DM with HFpEF, this study examines a different group of patients and explores GLP-1, which acts quite differently from glucagon biologically and in regard to the pathogenesis of heart failure. By targeting GLP-1, our study provides more detailed information on the multifactorial mechanisms linking diabetes and HFpEF and thus complements and extends the findings of our previous work.

Echocardiography and Biochemical measurement: All patients underwent transthoracic echocardiography to exclude HFpEF, HFmrEF, HF due to valvular heart disorders, cardiomyopathy (e.g., infectious or toxic), and cor-pulmonale. Echocardiography was used to evaluate left ventricular ejection fraction (LVEF), pulmonary artery systolic pressure (PASP), and E/e′. HFpEF was diagnosed based on clinical symptoms and signs of heart failure despite normal or near-normal LVEF (≥50%). Recognizing the challenges in

diagnosing HFpEF, we utilized the H2FPEF probability score to refine the diagnosis (Table 1) (12). However, the diagnosis was not reliant solely on the score; it was corroborated with echocardiographic and clinical data.

E/e′ and PASP values are components of the H2FPEF score but do not independently confirm or exclude the diagnosis of HFpEF. Patients may still meet the criteria for HFpEF even if these values are within the upper normal range. This reflects the heterogeneous pathophysiology of HFpEF, especially in diabetic patients, where subclinical diastolic dysfunction and elevated filling pressures are common. All patients experienced routine laboratory investigations as well as HbA1c. Fasting levels of serum GLP-1 were measured, after eight hours of fasting, using human double-antibody sandwich enzyme-linked immunosorbent assay (ELISA) kits supplied by SunRed®Company.

Ethics approval and consent to participate: This study protocol was approved by the Institutional Review Board (IRB), Faculty of Medicine, Zagazig University, Egypt, before the study was conducted (registration no. IRB #5801/15-12-2019). Written Informed consent was taken from the patients involved in this study. This work followed the regulations of the Declaration of Helsinki.

Statistical analysis All data were analyzed using MedCalc Statistical Software version 15.8 (MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org; 2015). Continuous variables were expressed as mean ± SD if normally distributed and median and range if not normally distributed. Continuous variables were checked for normality by using the Kolmogorov Smirnov test. The categorical variables were expressed as number and percentage. One-Way ANOVA was used to compare normally distributed variables in three or more groups. The Kruskal-Wallis H (KW) test was used to compare non-normally distributed variables in three or more groups. Post-hoc Fisher's Least Significant Difference test (LSD) was used according to homogeneity of variances to compare each two groups after comparing all groups using One-Way ANOVA. Pair-wise comparisons were used to compare each two groups after comparing all groups using Kruskal-Wallis H (KW) test. Percent of categorical variables were compared using the Chi-square ($\chi 2$) test. Spearman's rank correlation coefficient (Spearman's rho) was calculated to assess correlation between HFpEF and our study parameters. To measure the strength of association between dependent continuous variables and other independent ones, linear stepwise regression analysis was used. Receiver operating characteristic (ROC) curve analysis was used to identify optimal cut-off values of serum GLP-1 (pmol/L) for prediction of HFpEF in patients with type 2 DM. $p < 0.05$ was considered statistically significant (S) and $p \geq 0.05$ was considered non statistically significant (NS).

Results

In this study, 48 individuals were involved [27 male (56.2%) and 21 female (43.8%)]. Fifteen subjects (31.2%) were smokers, however 33 (69.8%) were nonsmokers. Patients with hypertension were 27(56.2%), in opposite to 21 (43.8%) non-hypertensives. The mean duration of diabetes among group II and III was 7.6 ± 6.3 years. Among patients with diabetes 24 patients were on insulin therapy however there was eight patients were treated with oral hypoglycemic drugs.

We compared our study subjects as regards the basic demographic parameters as well as the laboratory data which were summarized in **Table (2)** and **(3),** respectively.

Regarding glycemic parameters, Kruskal-Wallis H test showed that there was a statistically significant difference in fasting plasma glucose (FPG), and 2-hour postprandial plasma glucose (2hPPG) between the three studied groups X^2= (26.46, 18.17, respectively), p= (0.0001, 0.0001, respectively), with a mean FPG of 92.43 for Group I, 178.87 for Group II, and 170.56 for Group III, while the mean 2hPPG of 144 for Group I, 235.43 for Group II, and 204.8 for Group III. A Kruskal-Wallis H test showed that there was a statistically significant difference in HbA1C between the three studied groups X^2=32.3, p= 0.0001, with a mean HbA1C of 5.43 for Group I, 9.31 for Group II, and 8.162 for Group III.

A Kruskal-Wallis H test demonstrated that there was a statistically significant difference in H2FpEF score between the three studied groups X^2=37.85, p= 0.0001, with a mean of 1 for Group I, 3 for Group II, and 8 for Group III. The rest of Echocardiographic parameters recapped in **Table (4)**

Comparison of serum GLP-1(pmol/L) between the studied groups and LSD Post Hoc analysis were summarized in **Table (5)** and **(6),** respectively, as well as **Figure (1)**.

We studied the correlation between H2FPEF score and the different study parameters among individuals with diabetes (Group II and III). A negative correlation between H2FPEF Score and fasting GLP-1 (pmol/L) was detected (n= 32, r = -0.386, *P* < 0.00291), **Figure (2)**.

In univariable logistic regression analysis model to assess predictors of HFpEF among patients with type 2 DM, GLP-1 was the only predictor for HFpEF among diabetic patients (Coefficients β = -0.39915, *p 0.0245*). Utilizing ROC curve, fasting GLP-1(pmol/L) at cut off value of ≤ 7.48 pmol/L, had AUC = 0.738, with sensitivity of 68.75 % and specificity of 75% in predicting the presence HFpEF, **Figure (3)**.

Table (1): H_2FPEF score and probability of having HFpEF (11)

	Clinical Variable	**Values**	**Points**
H_2	***Heavy***	Body mass index > 30 kg/m^2	**2**
	Hypertensive	2 or more antihypertensive drugs	**1**
F	***Atrial Fibrillation***	Paroxysmal or persistent	**3**
P	***Pulmonary Hypertension***	Doppler echocardiographic estimated pulmonary systolic artery pressure >35 mm Hg	**1**
E	***Elder***	Age > 60 years	**1**
F	***Filling pressure***	E/e´ > 9	**1**
H_2FPEF score	**H_2FPEF score of 0–1: low probability (<20%),** **H_2FPEF score of 2–5 : intermediate probability,** **H_2FPEF score of 6–9: High probability (>90%), HFpEF is likely.**		**Sum (0–9)**

Table (2): Demographic and clinical data in studied groups:

	Group I		***Group II***		***Group III***		**Test**	**P**
	Control (n=16)		**Diabetic without HF (n=16)**		**Diabetic with HFpEF (n=16)**			
	No	**%**	**No**	**%**	**No**	**%**		
Age (Years) *Mean± SD* *Median (Range)*	51.3 ± 15.34 48.5 (32 – 80)		62.06 ± 8.33 61 (43 – 74)		64.8 ± 9.92 64 (47 – 80)		**KW** 8.22	**0.016 (S)**
Sex *Male* *Female*	12 4	75% 25%	9 7	56.2% 43.7%	6 10	37.5% 62.5%	χ^2 4.57	0.10 (NS)
Past History								
Smoking Status *Non Smoker* *Smoker*	9 7	56.2% 43.7%	11 5	68.7% 31.2%	13 3	81.2% 18.8%	χ^2 2.32	0.312 (NS)
HTN *No* *Yes*	16 0	100% 0%	5 11	31.2% 68.7%	0 16	0% 100%	χ^2 34.0	**<0.0001 (HS)**
Diabetes duration (Years) *Mean± SD* *Median (Range)*			12.18 ± 4.18 61 (43 – 74)		10.81 ± 3.88 64 (47 – 80)		**T** -0.96	0.34 (NS)
BMI *Mean± SD* *Median (Range)*	29.42 ± 3.5 28.5 (25.1 – 35.9)		32.85 ± 7.66 30.98 (22.86 – 46.6)		36.98 ± 6.9 34.8 (30.12 –55.25)		**KW** 11.4	**0.003 (HS)**

Table (3): Basic laboratory data of the studied population (n=32):

	Group I	*Group II*	*Group III*	Test	P	LSD Post Hoc analysis
	Control (n=16)	**Diabetic without HF (n=16)**	**Diabetic with HFpEF (n=16)**			
WBC ($x10^3/mm^3$) *Mean± SD* *Median (Range)*	7.62 ± 1.65 8 (4.6 – 10.2)	10.75 ± 3.64 10.85 (4.2 – 18.4)	11.44 ± 3.07 10.7 (7.4 – 17)	**F** 7.80	**0.001 (HS)**	**(I) & (II)** **(I) & (III)**
Hemoglobin (g/dl) *Mean± SD* *Median (Range)*	14 ± 0.96 13.8 (12.3 – 15.2)	11.88 ± 1.71 12.15 (9 – 14.6)	11.7 ± 2.18 11.8 (9.2 – 15.4)	**F** 9.0	**<0.001 (HS)**	**(I) & (II)** **(I) & (III)**
Platelet count ($x10^3/mm^3$) *Mean± SD* *Median (Range)*	280.4 ± 65.3 272 (199 – 410)	281.87 ± 139.5 245 (145 – 562)	284.43 ± 136.97 241 (134 – 673)	**KW** 0.666	0.71 (NS)	
Creatinine (mg/dl) *Mean± SD* *Median (Range)*	0.88 ± 0.18 0.86 (0.6 – 1.2)	1.2 ± 0.50 1.05 (0.57 – 2.15)	1.18 ± 0.53 1.05 (0.71 – 2.88)	**KW** 4	0.134 (NS)	
ALT (U/L) *Mean± SD* *Median (Range)*	22.23 ± 6 20 (12 – 34.5)	25.78 ± 21.8 20 (7 – 95)	49.1 ± 101.5 24.65 (4 – 427)	**KW** 0.46	0.79 (NS)	
AST (U/L) *Mean± SD* *Median (Range)*	28.9 ± 8.2 29.5 (12.2 – 40)	28.22 ± 20.2 20.8 (4.8 – 75)	24.96 ± 14.9 22.0 (8 – 60)	**F** 0.310	0.7 (NS)	
Albumin (g/dL) *Mean± SD* *Median (Range)*	4.26 ± 0.45 4.3 (3 – 4.8)	3.59 ± 0.60 3.68 (2.5 – 4.9)	3.53 ± 0.62 3.5 (2.4 – 4.36)	**F** 8.25	**0.001 (HS)**	**(I) & (II)** **(I) & (III)**

Table (4) Comparison of ECHO parameters between the studied groups (n= 48):

	Group I	*Group II*	*Group III*	Test	P
	Control (n=16)	**Diabetic without HF (n=16)**	**Diabetic with HFpEF (n=16)**		
EF *Mean± SD* *Median (Range)*	63.3 ± 2.54 63.5 (59 – 67)	64.5 ± 8.44 61.7 (50 – 84)	61.46 ± 4.68 61 (54 – 69)	**KW** 1.87	0.388 (NS)
E/e' *Mean± SD* *Median (Range)*	6.16 ± 0.8 5.95 (4.9 – 7.6)	8.75 ± 2.5 7.95 (4.87 – 13)	9.1 ± 0.88 9.1 (7.6 – 11.1)	**KW** 26.99	**<0.0001 (HS)**
PASP *Mean± SD* *Median (Range)*	26.6 ± 2.54 26.5 (22 – 31)	31.93 ± 7.28 30.45 (20 – 52)	35.72 ± 7.11 37.9 (22 – 46)	**KW** 13.5	**0.011 (S)**

Table (5): Comparison of serum GLP-1(pmol/L) between the studied groups (n = 48):

	Group I	*Group II*	*Group III*	Test	P
	Control (n=16)	**Diabetic without HF (n=16)**	**Diabetic with HFpEF (n=16)**		
GLP-1(pmol/L) *Mean± SD* *Median (Range)*	11.693 ± 2.047 11.74 (7.2– 15.44)	9.525 ± 3 8.98 (5.52 – 16.38)	7.197 ± 1.91 6.7 (5.05 – 10.5)	**F** 7..922	**<0.001 (HS)**

Table (6): LSD Post Hoc analysis of fasting serum GLP-1 level (pmol/L) between the studied groups (n = 48):

		Group I	*Group II*	*Group III*
Group I	**GLP-1**	-------	**0.013 (S)**	**0.0001 (HS)**
Group II		-------	-------	**0.008 (S)**

Figure (1) Serum GLP-1 levels (pmol/L) in the different study groups

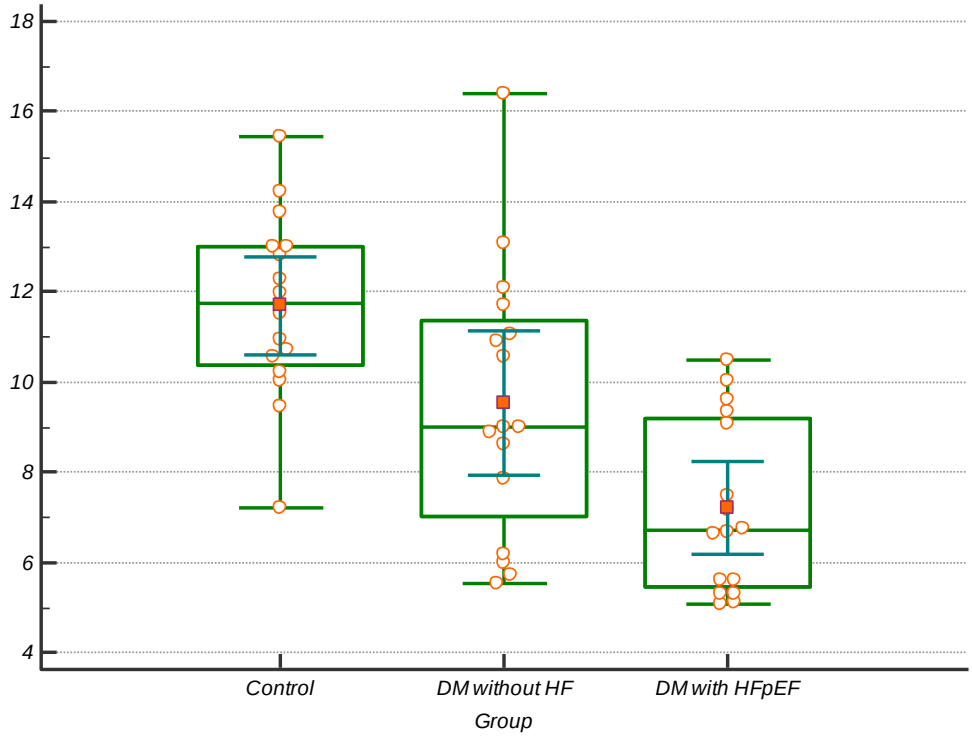


Figure (2): Correlation between HFpEF score and fasting GLP-1 (pmol/L) among diabetic population

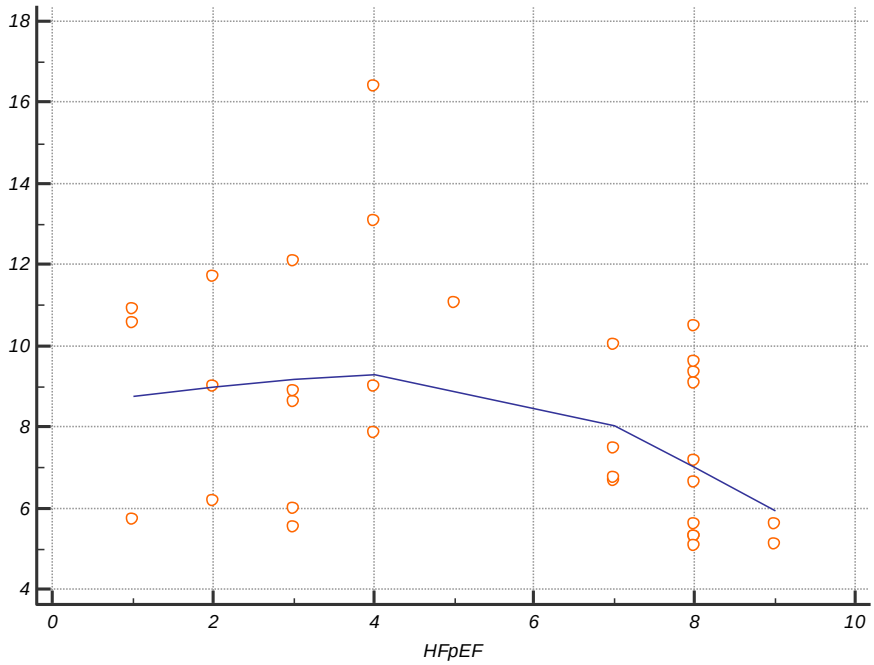
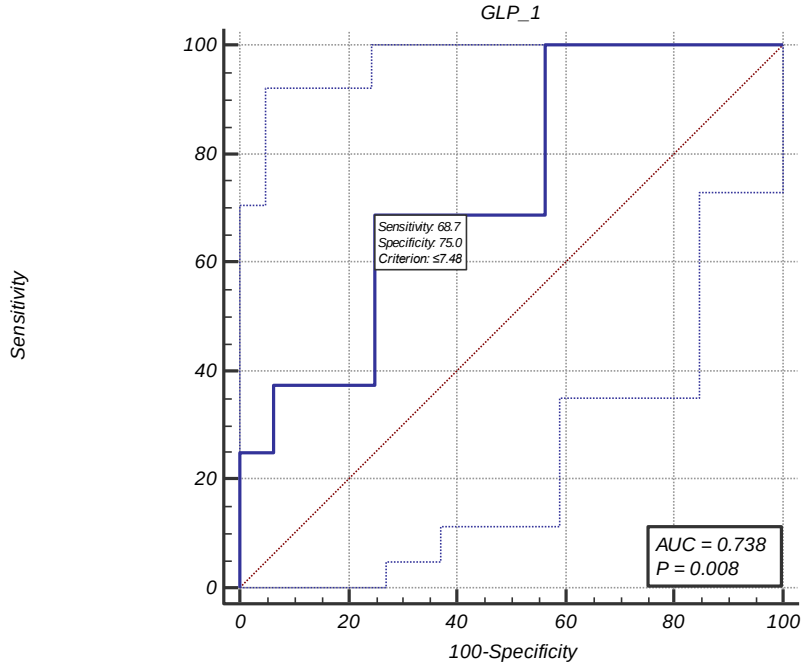


Figure (3): ROC curve of serum GLP-1(pmol/L) as a predictor of HFpEF among diabetic population



Discussion

Heart failure (HF) is a clinical syndrome conjoined with poor quality of life, considerable healthcare resource utilization, and premature mortality **(13)**. Ejection fraction is the cornerstone in identifying individuals with HF due to differences in co-morbid conditions, demographics, and response to therapy across different patients. **(14)**. HFpEF is diagnosed in patients with preserved left ventricular EF (LVEF ≥ 50%); with proof of diastolic dysfunction or structural heart disease, in the context of characteristic signs and symptoms of HF and elevated natriuretic peptides **(6)**. In patients with symptomatic HF, studies estimated that the prevalence of HFpEF is about 50% (range 40% to 71%). **(15)**. Cardiac dysfunction affects up to 35% of those with type 2 diabetes **(16)**. Type 2 diabetes is more closely related to the progression of HFpEF than HFrEF **(17)**. The pathological evolution of

new-onset HF in DM has been attributed to hyperglycemia's direct injurious effect and relevant metabolic consequences on the myocardium (diabetic cardiomyopathy), which often coexist with hypertension, coronary microvascular disease (CMD), and diabetic nephropathy **(18)**.

GLP-1 is a member of the pro-glucagon incretin family that regulates appetite and satiety **(19)**. GLP-1 functions via the GLP-1 receptor (GLP-1R), a 463 amino acid member of the G protein-coupled receptor (GPCR) superfamily **(20)**.

The GLP-1 receptor exists in many tissues, including the brain, pancreas, intestines, lungs, stomach, and kidney. GLP-1 possesses insulinotropic, insulinomimetic, and glucagonostatic properties, allowing it to play various complementary roles in lowering blood glucose in patients with type 2 diabetes. GLP-1 receptor agonists have attracted interest as an eventual treatment for diabetes, heart disease, and obesity. A large number of studies have pointed to the favorable effects of GLP-1 on CV function, which appears to warrant its use in the treatment of CV diseases **(21)**.

In this study, we aimed to assess the role of GLP-1 in HFpEF development among patients with type 2 diabetes mellitus.

Fasting serum GLP-1 was measured in the studied population. There was a significant difference between the studied groups. On post hoc analysis, the significance was between each group and the others. GLP-1(pmol/L) was 11.693 ± 2.047 in the control group, 9.525 ± 3 in the diabetic without HF group, and 7.197 ± 1.91 in the diabetic with HFpEF group. These results were in line with ***Combettes, (2006)*** who stated that in diabetic patients, GLP-1 secretion and action are impaired; GLP-1 effect is decreased to 30% **(22)**.

The important finding in the current study was the significant decline in GLP-1 in diabetics with HFpEF when compared with diabetics without HF. ***Nguyen et al, (2018)*** investigated for the first time the effects of long-term in vivo GLP-1 treatment in HFpEF induced by pressure overload in rats. ***Nguyen et al, (2018)***, found that GLP-1 could reduce diastolic dysfunction, left ventricular stiffness, and pulmonary congestion and concluded that GLP-1 presents a new promising therapeutic approach for HFpEF **(23)**.

The absence of sufficient studies investigating the role of GLP-1 in diabetics with HFpEF, and the lack of trials studying the effects of GLP-1 RAs on HFpEF in humans, prompted ***Belli et al, (2022)*** to address the current knowledge on the cardiac effects and potential benefits of GLP-1RAs in patients with HFpEF in his review. ***Belli et al, (2022)*** stated that GLP-1 RAs have positive CV effects. In previous randomized controlled trials with patients with type 2 DM, liraglutide, semaglutide, and dulaglutide have been shown to reduce CV mortality, but not the incidence of HF or hospitalization for HF. A growing body of evidence suggests a considerable positive effect of GLP-1 receptor agonists on LV diastolic function in patients with type 2 DM **(24)**.

On investigating the correlation between H2FPEF score and GLP-1, we found a statistically significant negative correlation between them among population with type 2 DM. This could be explained in the light of many studies that have proven the beneficial role of GLP-1infusion as a therapeutic option for HF patients. ***Sokos et al., (2006)*** clinical study had shown that 7-36 amide GLP-1 infusion improves the left ventricular ejection fraction and enhances functional capacity in patients with chronic heart failure **(25)**.

In univariable logistic regression analysis model to assess predictors of HFpEF among patients with type 2 DM, GLP-1 was the only predictor for HFpEF among diabetic patients (Coefficients $\beta = -0.39915$, *p 0.0245*). This means that the decline in GLP-1 might have a pathogenic relation to HFpEF development among patients with type 2 DM. Utilizing ROC curve, fasting GLP-1 (pmol/L) at cut-off value ≤ 7.48 (pmol/L), had AUC = 0.738, with sensitivity of 68.75 %, and specificity of 75 % in predicting the probability of HFpEF among type 2 diabetes patients.

Our study has some strengths and weaknesses. The study's strengths lie in its innovative approach to investigating the role of GLP-1 in HFpEF among Type 2 DM patients, employing a robust case-control design and interdisciplinary collaboration, which enhances the clinical relevance of the findings. However, limitations include a small sample size that may affect generalizability, a lack of long-term data, potential biases from a single study location, and a narrow focus on one biomarker without considering others that may influence HFpEF in Type 2 DM patients. These factors should be considered when interpreting the results and planning future research directions.

Conclusion When compared to individuals without HF, diabetic patients with HFpEF had significantly lower fasting serum GLP-1 levels. Low GLP-1 levels may increase the probability of developing HFpEF in type 2 diabetic patients; this suggests a causal relationship between GLP-1 decline and HFpEF development. Furthermore, in

the logistic regression analysis model, GLP-1 was the only independent predictor of HFpEF in diabetes patients. This could indicate that GLP-1 agonists are effective in the treatment of HFpEF. As a result, the therapeutic effect of GLP-1 agonists in HFpEF treatment should be investigated more thoroughly using therapeutic mega-trials.

List of abbreviations:

GLP1: glucagon like peptide 1, HF: Heart Failure, HFpEF: Heart Failure with preserved ejection fraction, HFrEF: Heart Failure with reduced ejection fraction, HFmrEF: Heart Failure with mild reduced ejection fraction, DM: diabetes mellitus, CV: cardiovascular, LVEF: left ventricular ejection fraction, HbA1c: hemoglobin A1c.

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