Prevalence of Prediabetes and Newly diagnosed Diabetes in Patients with HFpEF and HFrEF

Ahmad ELSharawy[a], Heba Saber Abdel Kader Hussein[a]*, Nayl Abdul Hameed Zaki[a] , Hassan Ahmad Hasanien[a]

[a]Department of Internal Medicine, Faculty of Medicine, Sohag University, Sohag, Egypt

Abstract

Background: New-onset heart failure (HF) and diabetes mellitus (DM) are both significant risk factors for each other.

Objectives: This study aims to determine the prevalence of prediabetic dysglycemia and Newly diagnosed diabetes among individuals with established CHF stratified by HFrEF or HFpEF.

Patients and methods: A total of 450 patients presented by HF admitted at Sohag university hospital, internal medicine department and CCU from October 2021 to December 2022 were screened for enrollment in this prospective study.All agreed to participate in this prospective study, 260 patient were excluded as they were Known to be diabetic. After that, 190 patients not known to be diabetic presented by CHF , then classified according HbA1C into 3 main groups Normoglycemic (with HbA1c less than 5.7), prediabetic (with HbA1c between 5.7 to 6.4) and newly diagnosed diabetic(with HbA1c more than 6.4) then the patients classified according to echocardiographic finding of LVEF into three groups: HFrEF patients with EF ≤ 40%, HFmrEF patients with EF between 41 to 49%,while HFpEF patients with EF ≥50.

Results: This study included 190 patients with confirmed diagnosis of CHF then HbA1c was measured in the studied 190 patients (don't known to be diabetic) who were divided into three groups (normoglycemic, prediabetic, and newly diagnosed diabetic). To find that 43 patients (22.6%) were normoglycemic with a HbA1c less than 5.7, 46 patients (24.2%) were prediabetics with a HbA1c between 5.7 and 6.4, and 101 patients (53.2%) were diabetics with a HbA1c greater than 6.4, indicating that both prediabetes and newly diagnosed diabetes are more common than normoglycemia in CHF patients.

Conclusion: The prevalence of prediabetes and recently diagnosed diabetes in HFrEF, HFmrEF, and HFpEF groups varied significantly from one another. Even before diabetes is identified and glucose-lowering medication is started, dysglycemia is associated with a greater risk of unfavorable clinical outcomes in individuals with both HFpEF and HFrEF.

Keywords: Heart failure; Prediabetes; Newly diagnosed diabetes.

DOI: 10.21608/svuijm.2023.227838.1646

***Correspondence:** heba011214@med.sohag.edu.eg

Received: 28 August, 2023.

Revised: 29 September, 2023.

Accepted: 30 September, 2023.

Published: 30 December, 2023

Cite this article as: Ahmad ELSharawy, Heba Saber Abdel Kader Hussein, Nayl Abdul Hameed Zaki , Hassan Ahmad Hasanien (2024). Prevalence of Prediabetes and Newly diagnosed Diabetes in Patients with HFpEF and HFrEF. *SVU-International Journal of Medical Sciences*. Vol.7, Issue 1, pp: 106- 118 .

Introduction

Chronic heart failure (CHF) is a progressive, complex clinical syndrome with high rates of morbidity and mortality that, either on its own or in combination with other comorbid conditions like diabetes mellitus (DM), causes a wide range of cardiovascular damages and early death. **(Dauriz et al., 2017)**

Cardiovascular illness, particularly heart failure (HF), is significantly increased by type 2 diabetes, and both conditions increases the risk of death. **(Emerging Risk Factors Collaboration, 2010)**

Diabetic patients are more likely to have heart failure (HF) than normoglycemics or non-diabetics , and those with both have worse outcomes than non-diabetics with HF . **(Kristensen et al., 2017)**

Recently, it was found that patients with HF who had either reduced ejection fraction (HFrEF) or preserved ejection fraction (HFpEF) frequently had either not diagnosed diabetes or prediabetes, both of which were predictive of worse outcomes than normoglycemia. **(Kristensen et al., 2016)**

Myocardial Glucose Uptake is lowered in segments with preserved Myocardial Flow Rate in CHF patients with prediabetes and newly diagnosed T2D. Thus, compared to patients with standard glucose tolerance, early diabetic and prediabetic CHF patients exhibit cardiac glucometabolic changes that may be involved during the disease. This contributes to the poor prognosis of these patients. **(Nielsen et al., 2018)**

75% of T2DM patients have diastolic dysfunction, which commonly appears in the early stages of the disease. Diastolic dysfunction severity is correlated with cardiovascular mortality, dysregulated carbohydrate metabolism, and CHF prevalence. **(Mamedov et al., 2018)**

The majority of T2DM patients develop HFpEF. The key factor contributing to the development of HFrEF in T2DM patients is concomitant CAD, which is more likely to occur in this population. **(Johansson et al., 2016)**

Since HFpEF often develops in the early stages of T2DM while HFrEF develops in more advanced T2DM, the degree of hyperglycemia plays a crucial role in the development of left ventricular dysfunction. **(Targher et al., 2016; Zinman et al., 2015)**

Patients and methods

This is an observational prospective study was conducted at Sohag University hospital, Internal Medicine department, and Coronary care unit (CCU) during the period from October 2021-December 2022. The study protocol was approved by the Ethics Committee of Sohag Faculty of Medicine. Written informed consent was obtained from all participants.

A total of 450 patients presented by HF admitted at Sohag university hospital, internal medicine department and CCU from October 2021 to December 2022 were screened for enrollment in this prospective study.All agreed to participate in this prospective study, 260 patient were excluded as they were Known to be diabetic. After that, 190 patients not known to be diabetic presented by CHF , then classified according HbA1C into 3 main groups Normoglycemic (with HbA1c less than 5.7), prediabetic (with HbA1c between 5.7 to 6.4) and newly diagnosed diabetic(with HbA1c more than 6.4) then the patients classified according to echocardiographic finding of LVEF into three groups: **HFrEF** patients with EF ≤ 40%, **HFmrEF** patients with EF between 41 to 49%,while **HFpEF** patients with EF ≥50

We excluded patients with CHF who have Overt T2DM , RHD and Congenital heart disease

All patients included in the study subjected to Full history taking, Detailed clinical examination, Laboratory investigations (FBG , 2h Post prandial glucose level, Hb A1c ,CBC, Liver function, Kidney function,Lipid profil) and imaging (ECG, Echocardiography)

Statistical analysis

The statistical analysis was performed using (SPSS, Inc., Chicagho, IL), Version 20.0 (IBM SPSS STATISTICS0.). Quantitative data is represented as mean ± standard deviation (SD) and pearson x2 test or fisher exact test is used to comparing differences of dichotomous variables.

The normality of variables was checked using the Shapiro-wilk test. Parametric test (t-test) is used for the assessment of differences between numerical variables with normal distribution. Accordingly, the nonparametric test (Mann whitney u-test) was used to compare mean between the two categorical groups and the Kruskall-wallis test for more than two groups) when datasets was found to be not normally distributed. Kaplan-Meier plots were presented for the time from admission to each of the major composite outcomes and deaths for the patient subgroups. The figures were performed using the GraphPad Prism software package, version 5.02 (San Diego, CA). Statistical significance is assumed at the P-value was 0.5 in all analysis.

Results

This prospective cohort study was carried out on 190 after exclusion of 260 patients (they have overt T2DM) from atotal 450 patients presented by heart failure, referred to Sohag University Hospital, department of internal medicine and CCU in the duration of the study for studing the prevalence of prediabetic dysglycemia and newly diagnosed diabetes among individuals with CHF not known to be diabetic Those patients were stratified according to LVEF to HFrEF or HFmrEF or HFpEF.

Patient demographics and descriptive data

Baseline characteristics of the study cohort are presented in (**Table.1**). 190 patients were included with age ranged between 20 years and 90 years with mean age was 61.97 (±13.56) years. there were 122 (64.2%) males and 68 (35.8%) females with male to female ratio was 1.79:1.

All patients not known to be diabetic, but as regard the other risk factors 80 patients (42.1%) were smokers. Hypertension was found in 59 (31.1%) patients. Most cases 89 patients (46.8%) presented by NYHA class III, 45.3% of them had NYHA class IV and 7.9% of them were NYHA class II. More than half of them (52.6%) were known cardiac patients. with the majority of them (42.1%) had ischemic heart disease. Only 4 patients (2.1%) were had prior CABG while 16 patients (8.4%) ha prior AF.

As regard the medical history, the most common drugs used was beta blockers in 98 (51.6%) patients followed by loop diuretics in 83 (43.7%) patients then RAAS blockers in 52 (27.4%) patients and digoxin in 5 (2.6%) patients. The mean heart rate in the studied patients was 88.02± 16.41 beats/min., the mean systolic blood pressure was 118.05± 17.67 mm/Hg and the mean BMI was 24.95± 4.84 Kg/m2 .

As regard the ECHO findings cardiomyopathy was the most frequent finding in 79 (41.6%) patients followed by ischemic heart disease in 44 (23.2%) patients Echo. the mean ejection fraction was 44.16± 15.19 % and ranged from 20%- to 72% with 45.26% cases had EF≤ 40 % (HFrEF).

Table 1. Demographic and clinical characteristics in the studied patients.

Variables		Studied patients (N= 190)
Gender	**Male / Female**	122 (64.2%) / 68 (35.8%)
Age (years)	**Mean± SD**	61.97± 13.56
	Median (Range)	65.0 (20.0 – 90.0)
Smoking	**No**	110 (57.9%)
	Yes	80 (42.1%)
Hypertension	**No**	131 (68.9%)
	Yes	59 (31.1%)
NYHA class	**Class II**	15 (7.9%)
	Class III	89 (46.8%)
	Class IV	86 (45.3%)

Known cardiac?	**No**	90 (47.4%)
	Yes	100 (52.6%)
Causes of CHF	**Not Known**	90 (47.4%)
	ICM	8 (4.3%)
	IDCM	12 (6.3%)
	IHD	80 (42.1%)
Prior CABG	**No**	186 (97.9%)
	Yes	4 (2.1%)
Prior AF	**No**	174 (91.6%)
	Yes	16 (8.4%)
B blocker	**No**	92 (48.4%)
	Yes	98 (51.6%)
RAAS inhibitors	**No**	138 (72.6%)
	Yes	52 (27.4%)
Digoxin	**No**	185 (97.4%)
	Yes	5 (2.6%)
Loop diuretics	**No**	107 (56.3%)
	Yes	83 (43.7%)
Echo findings	**SWMA/Hypokinesia**	36 (18.9%)
	Dyskinesia	4 (2.1%)
	CM	79 (41.6%)
	Dilated LA	3 (1.6%)
	LVH	24 (12.6%)
	IHD	44 (23.2%)
EF (%)	**≤ 40 % (HFrEF)**	86 (45.26%)
	41% – 49% (HFmrEF)	25 (13.16%)
	≥ 50 % (HFpEF)	79 (41.6%)
	Mean± SD	44.16± 15.19
	Median	44.5
	Range	20.0 – 72.0

Outcome Data and Main Results

AS regard the lab finding of HbA1C we found that the mean HbA1C was 6.75±1.17 and according to A1C finding the studied patients were divided into three groups: 43 patients (22.6%) were normoglycemic with HbA1c less than 5.7, 46 patients (24.2%) were prediabetics with HbA1c between 5.7 to 6.4 while 101 patients (53.2%) were diabetics with HbA1c more than 6.4. To find that prediabetes and newly diagnosed diabetes more prevalent in CHF than normoglycemia (**Fig.1).**

According To ECHO finding of LVEF the studied patients were classified into 3 groups : HFrEF 86(45.26%) patients with EF ≤ 40%,HFmrEF: 25(13.16%) patients with EF between 41 to 49% and HFpEF: 79 (41.6%) patients with EF ≥50%

Classification of the patients according to HbA1c on admission

As regard the relation between HbA1C and different categorical parameters, (**Table.2)** shows that There was significant difference between the three groups regarding gender (p=0.004) as prediabetics and diabetic status were significantly higher in males. There was significant difference between the three groups regarding age (p<0.001) as diabetes were significantly older than prediabetes, Smoking was more prevalent in patients with prediabetes and neely diagnosed diabetes than normoglycemic patients.

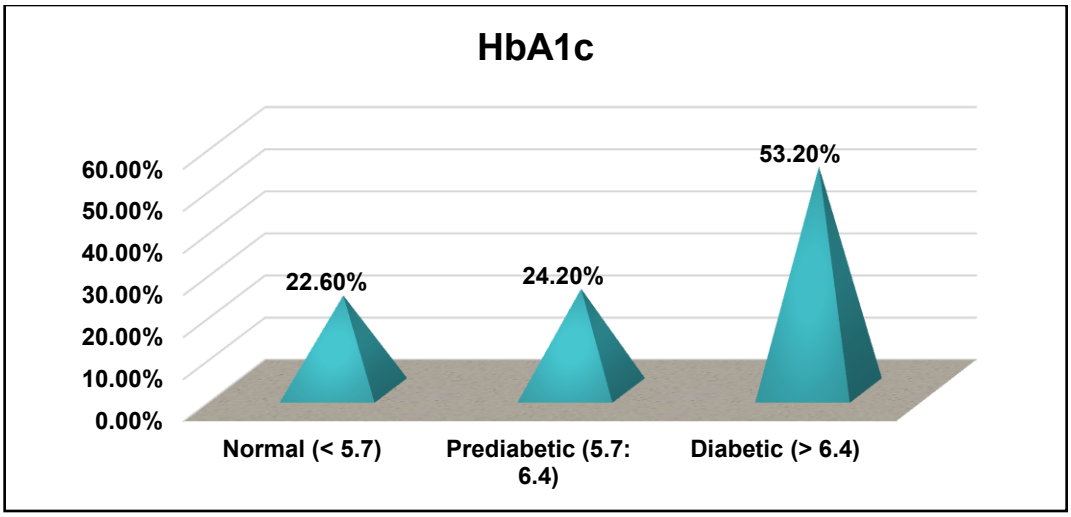

Fig.1. Distribution of studied patients regarding HbA1c.

Table 2. Clinical characteristics of the patients according to HbA1c

Parameters		Normoglycemic (n=43)	Prediabetics (n=46)	Diabetics (n= 101)	P-value
Age (years)	**Mean± SD**	58.48± 13.47	59.35± 16.82	66.54± 11.24	**<0.001**
	Median (Range)	60(20.0 – 80)	65(29.0 – 80.0)	68(38.0 – 90.0)	
Gender	**Male**	20 (46.5%)	37 (80.4%)	65 (64.4%)	0.004
	Female	23 (53.5%)	9 (19.6%)	36 (35.6%)	
Smoking	**No**	31 (72.1%)	26 (56.5%)	53 (52.5%)	0.09
	Yes	12 (27.9%)	20 (43.5%)	48 (47.5%)	
HTN	**No**	28 (65.1%)	34 (73.9%)	69 (68.3%)	0.656
	Yes	15 (34.9%)	12 (26.1%)	32 (31.7%)	
NYHA class	**II**	14 (32.6%)	0 (0.0%)	1 (1.0%)	**<0.001**
	III	16 (37.2%)	26 (56.5%)	47 (46.5%)	
	IV	13 (30.2%)	20 (43.5%)	53 (52.5%)	
known cardiac	**No**	26 (60.5%)	35 (76.1%)	29 (28.7%)	**<0.001**
	Yes	17(39.5%)	11 (23.9%)	72 (71.3%)	
Prior CABG	**No**	43 (100.0%)	46 (100.0%)	97 (96.0%)	0.165
	Yes	0 (0.0%)	0 (0.0%)	4 (4.0%)	
Prior PCI	**No**	38 (88.4%)	45 (97.8%)	79 (78.2%)	0.006
	Yes	5 (11.6%)	1 (2.2%)	22 (21.8%)	
prior Stroke	**No**	39 (90.7%)	46 (100.0%)	85 (84.2%)	0.014
	Yes	4 (9.3%)	0 (0.0%)	16 (15.8%)	
Prior AF	**No**	39 (90.7%)	46 (100.0%)	89 (88.1%)	0.054
	Yes	4 (9.3%)	0 (0.0%)	12 (11.9%)	
B-blocker	**No**	23 (53.5%)	36 (78.3%)	33 (32.7%)	**<0.001**
	Yes	20 (46.5%)	10 (21.7%)	68 (67.3%)	
MRA	**No**	38 (88.4%)	37 (80.4%)	63 (62.4%)	0.002
	Yes	5 (11.6%)	9 (19.6%)	38 (37.6%)	

Digoxin	**No**	43 (100.0%)	41 (89.1%)	101 (100.0%)	**<0.001**
	Yes	0 (0.0%)	5 (10.9%)	0 (0.0%)	
Loop diuretics	**No**	34 (79.1%)	39 (84.8%)	34 (33.7%)	**<0.001**
	Yes	9 (20.9%)	7 (15.2%)	67 (66.3%)	

Patients with newly diagnosed diabetes had worse NYHA class, known cardiac and had a history of prior stroke, prior AF and prior PCI compared to those with normoglycemia. Also, patients with diabetes had greater use of B-blocker, MRA and loop diuretics compared to those with normoglycemia. Patients with prediabetes had a clinical picture in between individuals with newly diagnosed diabetes and those with normoglycemia.

There was significant difference between normoglycemic, prediabetics and diabetic groups regarding systolic blood pressure. Also, there was significant difference between them regarding serum Na, ionized Ca, FBG, ALT, AST, T. bilirubin, Albumin, HB, MCV, PLT as well as HbA1c. In addition, EF showed significant difference between normoglycemic, prediabetics and diabetic groups. (**Table.3).**

Table 3. Comparison between the studied groups regarding laboratory and imaging characteristics.

Parameters	**Normoglycemic (n=43)**		**Prediabetics (n=46)**		**Diabetics (n= 101)**		**P-value**
	Mean ± SD	**Median**	**Mean ± SD**	**Median**	**Mean ± SD**	**Median**	
General Examination							
HR	90.23 ± 8.69	90.00	83.57 ± 12.60	80.00	89.15 ± 19.96	89.00	0.056
SBP	110.47 ± 17.04	110.00	124.78 ± 20.08	125.00	118.22 ± 15.52	120.00	**<0.001**
BMI	25.28 ± 4.06	24.00	24.96 ± 4.52	25.00	24.81 ± 5.30	23.00	0.597
Laboratory investigations							
eGFR	65.44 ± 20.02	65.00	62.24 ± 16.41	66.00	57.03 ± 20.69	60.00	0.126
serum K	3.87 ± .28	4.00	3.88 ± .30	4.00	4.02 ± .59	4.00	0.319
serum Na	138.67 ± 4.40	139.00	135.72 ± 4.37	136.00	134.68 ± 5.36	136.00	**<0.001**
ionized Ca	1.04 ± .06	1.00	1.05 ± .09	1.10	1.02 ± .06	1.00	**0.013**
EF	50.74 ± 15.19	55.00	39.26 ± 13.53	39.00	43.58 ± 15.06	42.00	**0.001**
FBG	99.63 ± 11.17	100.00	128.98 ± 24.01	121.00	145.37 ± 49.18	130.00	**<0.001**
ALT	19.76 ± 8.86	16.00	32.29 ± 21.11	26.00	113.58 ± 48.97	20.00	**0.008**
AST	39.76 ± 38.22	27.00	79.57 ± 73.70	45.00	110.15±74.89	26.00	**0.011**
T.Bil	0.90 ± 0.30	1.00	0.91 ± 0.10	1.00	2.63±1.65	1.00	**0.006**
Albumin	3.78 ± 0.38	4.00	3.58 ± 0.92	4.00	3.59 ± 0.46	3.80	**0.014**
WBC	11.39 ± 5.23	10.00	11.10 ± 3.31	11.00	10.59 ± 3.92	11.00	0.854
HB	12.20 ± 1.69	12.00	14.01 ± 1.34	14.90	12.07 ± 2.22	12.00	**<0.001**
MCV	85.76 ± 6.22	88.00	88.33 ± 5.94	88.00	83.31 ± 4.47	81.50	**<0.001**
PLT	237.32 ± 70.11	232.00	291.33 ± 89.71	313.00	331.85 ± 318.17	277.00	**0.019**
HbA1c	5.56 ± 0.30	5.60	6.23 ± 0.17	6.30	7.48 ± 1.12	7.10	**<0.001**

HR = Heart Rate , SBP= Systolic blood pressure, BMI = Body Mass Index, eGFR = Estimated Glomerular Filtration Rate, EF = Ejection Fraction, FBG= Fasting Blood Glucose.

Based on echo finding as regard EF, We divided the studied patients into three groups: HFrEF: 86 patients with EF ≤ 40%, HFmrEF: 25 patients with EF between 41 to 49%,while HFpEF: 79 patients with EF ≥50%, there was significant difference between, HFrEF, HFmrEF and HFpEF groups regarding HbA1c classification (p<0.001) **(Fig.2)** as group with HFrEF had 15.1% cases were Normoglycemic, 27.9 % cases were prediabetics and 57% cases were newly diagnosed diabetics. Group with HFmrEF had 44% cases were prediabetics and 56% cases were newly diagnosed diabetics. While, group with HFpEF had 38% cases were Normoglycemic, 13.9% cases were prediabetics and 48.1% cases were newly diagnosed diabetics (**Table. 4**)

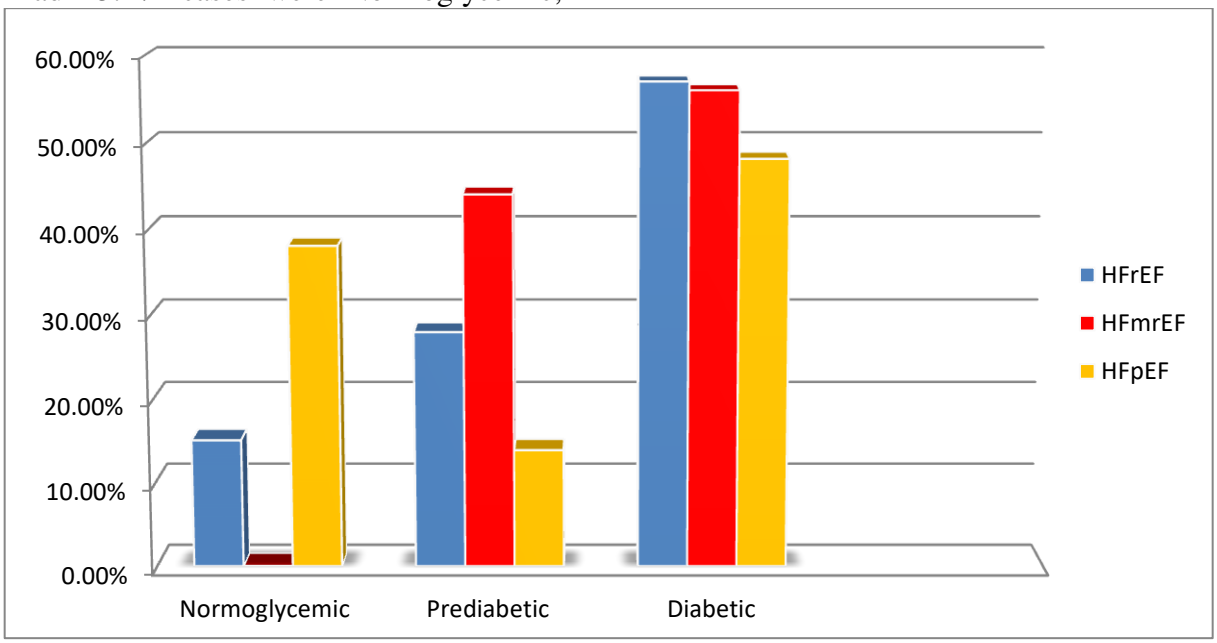

Fig.2. Relation between HbA1c classification and Echo finding as regard EF.

Table 4. Relation between HbA1c classification and Echo finding as regard EF.

Variables		HFrEF (n=86)	HFmrEF (n=25)		HFpEF (n=79)		P-value
		N (%)	N	%	N	%	
HbA1c	Normoglycemic	13 (15.1%)	0 (0.0%)		30 (38.0%)		<0.001
	Prediabetics	24 (27.9%)	11 (44%)		11 (13.9%)		
	Diabetics	49 (57.0%)	14 (56%)		38 (48.1%)		

Discussion

In people with diabetes, these complications increase mortality, cause blindness, cause renal failure, and lower quality of life. T2D is a prevalent metabolic condition that causes atherosclerotic cardiovascular disease and diabetic myocardiopathy. These disorders, in addition to myocardial infarction (MI) and chronic pressure overload, may cause heart failure through a variety of ways. **(De Rosa et al., 2018)**

People with diabetes are more likely to develop HF than people without diabetes, and those who already have HF are more likely to experience poorer outcomes. The latter finding is extremely important because co-existing diabetes is common in HF patients, impacting anywhere between 25 and 50% of people. **(Targher et al., 2017)**

Adults with a history of cardiovascular disease (CVD), hypertension (140/90 mmHg or taking medication for hypertension), triglyceride levels > 250 mg/dL (2.82 mmol/L), physical inactivity, and other clinical conditions linked to insulin resistance (e.g., extreme obesity, acanthosis nigricans) are risk factors for developing diabetes mellitus (DM). Additionally, people who have prediabetes and pregnant women with gestational diabetes mellitus are at risk for developing diabetes. Diabetes patients run the risk of both macrovascular problems like CVD and microvascular complications (such as diabetic kidney disease, diabetic retinopathy, and neuropathy). **(Cole and Florez, 2020)**

Two of the most significant epidemics of the modern era are HF and T2DM. The connections between the 2 circumstances are not entirely clear, despite the fact that each produces the other. The link between HF and the onset of DM is less clear, despite the fact that it is commonly accepted that DM is a risk factor for the development of HF and significantly raises the chance of worse outcomes if HF begins. Although insulin resistance appears to be a factor in HF, the underlying mechanisms are unclear. There are very few research that have looked at the prevalence of pre-diabetic dysglycemia in patients with heart failure and even fewer that have looked at its clinical effects (and with conflicting findings). **(Tomova et al., 2012)**

From two different angles, it is clinically significant to determine if pre-diabetes is associated, if at all, with negative clinical results. Hypoglycemic medications have recently raised concerns that they may be to blame for the poor cardiovascular outcomes, including HF, in patients with DM. The idea that dysglycemia per se is dangerous in HF would be supported by evidence showing that patients with pre-diabetes who are not treated with hypoglycemic medications have worse outcomes than those who are normoglycemic. **(McMurray et al., 2014)**

This prospective cohort study was carried out on 190 patients after exclusion of 260 patients (they have overt T2DM) from atotal 450 patients presented by CHF, aged 18 years or older, Classified according to NYHA classification from NYHA class 2 and more presented with HF. All patients included in the study were subjected to full history: personal history: age -sex -smoking, family history of cardiac diseases , medical history of: HTN, Ischemic heart disease, Prior CABG, Prior PCI, Prior Stroke, Prior AF, therapeutic history, Detailed clinical examination , Laboratory investigations (FBG, Hb A1c, CBC: HB, MCV, PLT, WBCs, Liver function, Kidney function, Lipid profile, ECG, Echocardiography.

This study revealed that the age of studied patients ranged between 20 years and 90 years with mean age was 61.97 (±13.56) years. Most patients (68.4%) were more than 60 years. there were 122 (64.2%) males and 68 (35.8%) females with male to female ratio was 1.79:1.80 patients (42.1%) were smokers. Hypertension was found in 59 (31.1%) patients while none of

patients was known to have DM. 7.9% of patients presented by NYHA class II ,46.8% Class III, 45.3% Class IV.

260 patients presented by CHF were excluded as they have overt T2DM to find that diabetes is a significant Risk factor and prevalent in CHF then HbA1c was measured in the studied 190 patients(don't known to be diabetic) who were divided into three groups(normoglycemic, prediabetic and newly diagnosed diabetic) To find that both prediabetes and newly diagnosed diabetes more prevalent than normoglycemia in CHF patient as 43 patients (22.6%) were normoglycemic with HbA1c less than 5.7, 46 patients (24.2%) were prediabetics with HbA1c between 5.7 to 6.4 while 101 patients (53.2%) were diabetics with HbA1c more than 6.4.

This study showed that patients with newly diagnosed diabetes older, had worse NYHA class and known cardiac and had a history of prior stroke, prior PCI compared to those with normoglycemia. Also, patients with diabetes had greater use of B-blocker, RAAS blockers and loop diuretics compared to those with normoglycemia. Patients with prediabetes had a clinical picture in between individuals with known diabetes and those with normoglycemia.

This results revealed that Based on echo finding as regard EF, We divided the studied patients into three groups: HFrEF: 86 patients with EF ≤ 40%, HFmrEF: 25 patients with EF between 41 to 49%, while HFpEF: 79 patients with EF ≥50% There was significant difference between, HFrEF, HFmrEF and HFpEF groups regarding HbA1c classification ($p<0.001$) as group with HFrEF had 15.1% cases were Normoglycemic, 27.9% cases were prediabetics and 57% cases were newly diagnosed diabetics. Group with HFmrEF had 44% cases were prediabetics and 56% cases were newly diagnosed diabetics.

It is widely acknowledged that HFpEF is a global public health issue. Older individuals with HFpEF are known to have a significant comorbidity burden, and its prevalence rises with age. Cardiovascular risk factors like hypertension, diabetes, obesity, and AF as well as non-cardiovascular disorders like chronic obstructive pulmonary disease and chronic renal disease are common comorbidities linked with HFpEF. **(Hedman Å et al., 2020)**

Through systemic microvascular inflammation and coronary microvascular dysfunction, which cause myocardial stiffness, fibrosis, and diastolic dysfunction, the high comorbidity burden is hypothesised to play a fundamental pathophysiological role in HFpEF. The frequency, incidence, and consequences of HFpEF vary by sex, ethnicity, and geographic location, according to earlier studies. In more recent times, cluster studies have given patients' groups with certain combinations of these traits and comorbidities the opportunity to be identified. These groups are thought to represent patients with similar pathophysiological causes. **(Segar et al., 2020)**

Diabetes is a significant risk factor for HFpEF patients. In the CHARM programme, 22% of patients with HFpEF were prediabetic, with a haemoglobin A1c between 6.0% and 6.4%, and 40% of patients with HFpEF had a diagnosis of diabetes upon enrollment. Additionally, according to epidemiological research, one-third of HFpEF patients had a diabetes diagnosis. In the pathophysiology underlying the development of HFpEF, oxidative stress, vascular inflammation, and endothelial dysfunction all play significant roles. Multiple pathways lead to oxidative stress in diabetic individuals, which increases the formation of reactive oxygen species (e.g. superoxide, hydrogen peroxide and hydroxyl radicals). **(American Diabetes Association Professional Practice, 2022)**.

Recently, it was discovered that patients with HFrEF frequently had

prediabetic dysglycemia and undiagnosed diabetes as well. Both conditions were linked to worse outcomes when compared to normoglycemia, though the risk was not as great as in patients with diagnosed diabetes. **(Kristensen et al., 2016)**

In the study by **Egstrup in 2011**, 227 ambulatory patients with HFrEF who were visiting a heart failure clinic in Denmark were assessed using the more accurate technique of oral glucose tolerance testing. In addition, 20% of the study cohort had DM with a diagnosis. Of those, 60% had normal glucose tolerance, 22% had impaired glucose tolerance, and 18% had DM without a diagnosis. The proportions of individuals with pre-diabetes mellitus (38%) and undiagnosed diabetes mellitus (20%) were both higher in a substantially bigger and geographically diversified group of patients without diabetes mellitus. This resulted in a startling 74% of the population having diabetes mellitus or pre-diabetes. **(Egstrup et al., 2011)**.

In the same context, **Kristensen in 2017** looked at 3023 patients aged 18 or older, in York Heart Association (NYHA) functional classes II to IV, with a baseline glycated haemoglobin measurement stratified by HFrEF or HFpEF, the prevalence and outcomes associated with normoglycemia, prediabetic dysglycemia, and diabetes (diagnosed and undiagnosed). They discovered that HbA1c was assessed at baseline in CHARM patients recruited in the United States and Canada, and that it was available in 1072/3023 (35%) of patients with HFpEF and 1578/4576 (34%) of patients with HFrEF. 20 and 22%, respectively, had prediabetes (HbA1c 6.0-6.4), while 18 and 16% had normoglycemia (HbA1c 6.0). Finally, among patients with HFpEF, 22% had diabetes that had not been diagnosed (HbA1c > 6.4) and 40% had diabetes that had been diagnosed (any HbA1c), compared to 26 and 35% among patients with HFrEF, respectively**. (Kristensen et al., 2017)**

Additionally, patients with known or undiagnosed diabetes were older, had a worse NYHA class distribution and kidney function, and were more likely to have coronary heart disease symptoms. **(Kristensen et al., 2016)**

In the same context, **Kristensen in 2016** looked at the clinical outcomes in 8399 patients with HFrEF based on history of DM and glycemic status (baseline haemoglobin A1c [HbA1c]<6.0% [42 mmol/mol], 6.0%-6.4% [42-47 mmol/mol; pre-diabetes mellitus], and ≥6.5% diabetes NYHA class II–IV symptoms and an EF of at least 40% (later amended to at least 35%) were the inclusion criteria for the PARADIGM–HF trial. It was discovered that patients with previously diagnosed diabetes mellitus had notable differences from those without, including older age, longer duration of heart failure, lower eGFR, and a higher frequency of ischemic causes (including prior myocardial infarction). **(Kristensen et al., 2016)**

While, group with HFpEF had 38% cases were Normoglycemic, 13.9% cases were prediabetics and 48.1% cases were newly diagnosed diabetics. The discovery of a similarly high proportion of dysglycemia in these two radically different phenotypes raises the possibility that the HF syndrome itself contributes to the emergence of prediabetes and diabetes. Notably, insulin resistance is found in both individuals with ischemic and idiopathic dilated cardiomyopathies. It is also more prevalent in patients with CAD and HF than in those without HF, and it is unrelated to ejection fraction. These results imply that the high prevalence of dysglycemia in HF is due to HF and not explained by known correlations, such as those with atherosclerosis. **(Swan et al., 1997)**

Additionally, a 2016 study by Kristensen found that only 18% of patients with HFpEF and 16% of patients with HFrEF were normoglycemic. In both kinds of HF, prediabetes was more prevalent than normoglycemia: 20% in patients with

HFpEF and 22% in those with HFrEF (p = 0.25). Patients with HFpEF had a lower incidence of undiagnosed diabetes than those with HFrEF (22 vs. 26%, p = 0.01) despite both conditions being highly prevalent. On the other hand, patients with HFpEF had a greater prevalence of recognized diabetes (40 vs. 35%, p = 0.02). As a result, 62% of people (diagnosed and previously undiagnosed) had diabetes of some kind. The fact that HbA1c was only measured in patients from North America, where diabetes prevalence is high, may help to explain this. According to the most recent data, 34% of the population has prediabetes, and 10% of the general population has diabetes, whether it is diagnosed or undiagnosed. **(Kristensen et al., 2016)**

The risk of developing pre-diabetes mellitus and diabetes mellitus was observed across the EF spectrum, however it was not statistically significant in individuals with EF >35% and tended to be more pronounced at lower EF, according to **Kristensen et al. (2016).** When we evaluated the risk of diabetes mellitus and pre-diabetes mellitus based on renal function, a similar pattern was seen**. (Kristensen et al., 2016)**

The prevalence of non-diabetic dysglycemia in HFrEF has only been recorded in a few earlier investigations. (27%) of the 663 patients in a substudy of the Randomized Evaluation of Strategies for Left Ventricular Dysfunction **(RESOLVD)** pilot study described in one seminal article had DM. 11% had undetected diabetes mellitus (fasting plasma glucose ≥7.1 mmol/L).The remainder patients had a fasting glucose between 6.1 and 7.1 mmol/L diagnostic of impaired fasting glycemia, a pre-diabetic state,Also, **Son et in 2022** performed a prospective cross-sectional observational study with 190 non-overweight normotensive HF patients (114 with HFrEF and 76 with HFpEF, 92.6% of which were ischemic HF; mean age was 70.1 years; mean BMI was 19.7 kg/m2) without diabetes (neither known diabetes nor newly diagnosed by OGTT); and 95 healthy individuals (controls). According to the 2006 WHO criteria for defining prediabetes, it is more common and has a trend toward more severe IR in people with HFrEF than in people with HFpEF, which is linked to a more severe HF. **(Son et al., 2022)**

A subgroup analysis of the CHARM research on HF patients revealed a strikingly high frequency of dysglycemia, defined as HbA1c 6.0%, regardless of the ejection fraction profile, and a relationship between dysglycemia and a higher risk of unfavourable clinical outcomes. HbA1c 6.0% does not, however, currently represent a cut-off for dysglycemia and does not provide a precise diagnosis of glycemic status. **(Kristensen et al., 2017)**

Although it is well known that individuals with both HFrEF & HFpEF have a high prevalence of diabetes mellitus, it appears that these patients also frequently have pre-diabetes mellitus and undetected diabetes mellitus. A significantly elevated risk of negative outcomes is linked to non-diabetic dysglycemia (pre-diabetes mellitus) in HFrEF. However, whereas the risk of diabetes mellitus is well understood, that of pre-diabetes mellitus is not as well known.

Conclusion

Our study showed that the HFrEF, HFmrEF, and HFpEF groups differed significantly in terms of how prediabetes and newly diagnosed diabetes were common. In patients with both HFpEF and HFrEF, dysglycemia is linked to a higher risk of unfavourable clinical outcomes even before diabetes is diagnosed and glucose-lowering medication is started.

References

- **American Diabetes Association Professional Practice, C. (2022).** Classification and Diagnosis of Diabetes: Standards of Medical Care in

Diabetes-2022. Diabetes Care, 45, 17-38.

- **Cole JB , Florez JC. (2020).** Genetics of diabetes mellitus and diabetes complications. Nat Rev Nephrol, 16: 377-390.
- **De Rosa S, Arcidiacono B, Chiefari E, Brunetti A, Indolfi C, Foti DP. (2018).** Type 2 Diabetes Mellitus and Cardiovascular Disease: Genetic and Epigenetic Links. Front Endocrinol (Lausanne), 9: 2.
- **Egstrup M, Schou M, Gustafsson I, Kistorp CN, Hildebrandt PR , Tuxen CD. (2011).** Oral glucose tolerance testing in an outpatient heart failure clinic reveals a high proportion of undiagnosed diabetic patients with an adverse prognosis. Eur J Heart Fail, 13:319-26.
- **Emerging Risk Factors Collaboration. (2010).** Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. The lancet, 375(9733): 2215-2222.
- **Hedman ÅK, Hage C, Sharma A, Brosnan MJ, Buckbinder L, Gan LM, et al. (2020).** Identification of novel pheno-groups in heart failure with preserved ejection fraction using machine learning. Heart, 106: 342-349.
- **Johansson I, Dahlström U, Edner M, Näsman P, Rydén L, & Norhammar A. (2016).** Prognostic implications of type 2 diabetes mellitus in ischemic and nonischemic heart failure. Journal of the American College of Cardiology, 68(13): 1404-1416.
- **Kristensen S, Jhund P, Lee M, Køber L, Solomon S , Granger C, et al. (2017).** Prevalence of Prediabetes and Undiagnosed Diabetes in Patients with HFpEF and HFrEF and Associated Clinical Outcomes. Cardiovascular Drugs and Therapy, 31: 1-5.
- **Kristensen S, Preiss D, Jhund P, Squire I, Cardoso J, Merkely B, et al. (2016).** Risk Related to Pre–Diabetes Mellitus and Diabetes Mellitus in Heart Failure With Reduced Ejection Fraction. Circulation: Heart Failure, 9: e002560.
- **Mamedov M, Bondarenko I, Mareev Y, Kanorskii S, Khalimov Y & Agafonov P. (2018).** New statement on chronic heart failure in patients with diabetes mellitus of the Heart Failure Association of the European Society of Cardiology: comments of Russian experts. Международный журнал сердца и сосудистых заболеваний, 6(20 (eng)): 34-40.
- **Marco Dauriz, Giovanni Targher, Pier Luigi Temporelli, Donata Lucci, Lucio Gonzini, Gian Luigi Nicolosi, et al. (2017).** Prognostic impact of diabetes and prediabetes on survival outcomes in patients with chronic heart failure: a post-hoc analysis of the GISSI-HF (Gruppo Italiano per lo Studio della Sopravvivenza nella Insufficienza Cardiaca-Heart Failure) Trial. Journal of the American Heart Association, 6(7): e005156 .
- **McMurray J, Gerstein H, Holman R , Pfeffer M. (2014).** Heart failure: a cardiovascular outcome in diabetes that can no longer be ignored. Lancet Diabetes Endocrinol, 2: 843-51.
- **Nielsen R, Jorsal A, Iversen P, Tolbod L, Bouchelouche K, Sørensen J, et al. (2018).** Heart failure patients with prediabetes and newly diagnosed diabetes display abnormalities in myocardial metabolism. Journal of Nuclear Cardiology, 25: 169-176.
- **Segar M, Patel K, Ayers C, Basit M, Tang W, Willett D, et al. (2020).** Phenomapping of patients with heart failure with preserved ejection fraction using machine learning-based unsupervised cluster analysis. Eur J Heart Fail, 22: 148-158.
- **Son T, Toan N, Thang N, Le Trong Tuong H, Tien H, Thuy N, et al. (2022).** Prediabetes and insulin resistance in a population of patients with heart failure and reduced or preserved ejection fraction but without

diabetes, overweight or hypertension. Cardiovascular Diabetology, 21: 75.

- **Swan J, Anker S, Walton C, Godsland I, Clark A, Leyva F, et al. (1997).** Insulin resistance in chronic heart failure: relation to severity and etiology of heart failure. J Am Coll Cardiol, 30: 527-32.
- **Targher G, Dauriz M, Laroche C, Temporelli PL, Hassanein M, Seferovic PM, et al. (2017).** In-hospital and 1-year mortality associated with diabetes in patients with acute heart failure: results from the ESC-HFA Heart Failure Long-Term Registry. Eur J Heart Fail, 19: 54-65.
- **Targher G, Dauriz M, Tavazzi L, Temporelli PL, Lucci D, Urso R,et al. (2016).** Prognostic impact of in-hospital hyperglycemia in hospitalized patients with acute heart failure: Results of the IN-HF (Italian Network on Heart Failure) Outcome registry. International journal of cardiology, 203: 587-593.
- **Tomova GS, Nimbal V & Horwich TB. (2012).** Relation between hemoglobin a(1c) and outcomes in heart failure patients with and without diabetes mellitus. Am J Cardiol, 109: 1767-73.
- **Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, et al. (2015).** Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. New England Journal of Medicine, 373(22): 2117-2128