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Prevalence of Heart Failure Among Type 2 Diabetic Patients in Benha City, Egypt: A Hospital-Based Cross-Sectional Study

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ABSTRACT

Background: Diabetes mellitus is highly prevalent amongst patients with heart failure, especially those with heart failure and preserved ejection fraction (HFpEF), and patients with the two conditions have a higher risk of mortality compared with patients without diabetes or heart failure. The aim of the study is to determine the prevalence of heart failure among type 2 diabetic patients in Benha city, Egypt and to assess the different causes and risk factors of heart failure (HF) and the impact of glycemic control on the prevalence of HF as well as the effect of different anti-diabetic drugs on control of HF.

Patients and methods: This cross-sectional study was conducted on 200 patients with type 2 diabetes attending the outpatient and inpatient clinics of Benha teaching hospital. All included patients were subjected to full history taking, complete clinical examination and laboratory investigations.

Results: The prevalence of HF in diabetic patients was 35.5% [28 (39.4%) females and 43 (60.6%) males], while patients without heart failure represented 64.5% [85 (65.9%) females and 44 (34.1%) males]. The mean age was 60 (SD 11) for patients with HF, and 58 (SD 11) years for those without HF. Glycemic control was significantly lower in those with HF (9.9%) than those without HF (68.2%), with $p<0.001$. Fasting blood glucose and HBA1c were significantly higher in those with HF failure than those without HF ($p<0.001$). The number of patients with HF who were on sulfonylurea and thiazolidinediones (TZD) was significantly higher than those without HF who were using them. **Conclusion:** There is a strong association between type 2 diabetes and both prevalent and incident HF. TZDs are not recommended in patients with symptomatic heart failure, and initiation of therapy is contraindicated in patients with established HF.

Keywords: Heart failure, Type 2 diabetes mellitus, thiazolidinediones, fasting blood glucose, HBA1c.

INTRODUCTION

Diabetes mellitus (DM) is highly prevalent amongst patients with heart failure (HF), especially those with HF and preserved ejection fraction (HFpEF), and patients with the two conditions have a higher risk of mortality compared with patients without DM or HF [(1)]. Diabetic patients have an increased risk of developing HF because of the abnormal cardiac handling of glucose and free fatty acids (FFAs), and because of the effect of the metabolic derangements of diabetes on the cardiovascular system. Furthermore, the metabolic risk of DM in HF is heightened by the effect of most anti-diabetic medications, as the use of certain anti-diabetic agents increase the risk of mortality and hospitalisation for HF both in patients with and without HF [(2)].

This effect may be related to a direct effect of the glucose-lowering molecules on the cardiovascular system and/or to a negative effect of excessive glucose lowering, since lenient glycaemic control with newer therapeutic agents has shown to reduce significantly mortality, morbidity and risk of developing HF in diabetic patients with proven cardiovascular disease [(3)].

A wealth of epidemiological evidence demonstrates that DM is independently associated with the risk of developing HF, with the risk increasing by more than two fold in men and by more than five fold in women [(4)].

HF is highly prevalent (25 % in chronic HF and up to 40 % in acute HF) in patients with DM. Its prevalence is four-times higher than that of the general population, suggesting a pathogenetic role of DM in HF. This pathogenetic role is also suggested by the fact that patients with DM and without HF have an increased risk of developing HF compared with a matched population (29 versus 18 %, respectively) [(5)].

In patients with DM, advanced age, duration of the disease, insulin use, presence of coronary artery disease and elevated serum creatinine are all independent risk factors for the development of HF [(6)].

HF and DM frequently co-exist in a bidirectional relationship as it is proposed by pathophysiological and epidemiological data. At the moment several pathophysiological connections have been proposed but we cannot definitively conclude on the pathophysiological mechanisms precipitating this complex interaction. Both entities are characterised by high morbidity and mortality, and treatment must target the overall improvement as DM treatment can decompensate HF and vice versa [(7)].

This study aimed to determine the prevalence of HF among type 2 diabetic patients in Benha city, Egypt and to assess the different causes and risk factors of HF and the impact of glycemic control on the prevalence of HF as well as the effect of different anti diabetic drugs on control of HF.

PATIENTS AND METHOD

This cross-sectional study was conducted on 200 patients with type 2 DM attending the outpatient and inpatient clinics of Benha Teaching Hospital.

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HF was diagnosed according to American Heart Association (AHA) Guidelines for the diagnosis and treatment of HF 2022. HF is defined, clinically, as a syndrome in which patients have typical symptoms (e.g. breathlessness, ankle swelling, and fatigue) and signs (e.g. elevated jugular venous pressure, pulmonary crackles, and displaced apex beat) resulting from an abnormality of cardiac structure or function [(8)].

The following diabetic patients were excluded from the study:

- Patients below 18 years.
- Type 1 diabetic patients.
- Patients who have other concomitant heart diseases e.g., rheumatic heart disease, congenital heart disease, corpulmonale, restrictive cardiomyopathy, HOCM.

All included patients were subjected to a complete interview and clinical examination with special stress on:

1. Symptom of HF.
2. Demographic characteristics including anthropometric parameters (weight, height, waist circumference, and BMI).
3. Systolic and diastolic blood pressure after a 5 minute rest.
4. Diabetic history (type and duration of diabetes, diabetic complications, anti diabetic drugs).
5. History of cardivascular diseases including previous diagnosis of HF, level of physical activity (low, medium, high) and treatment with cardiovascular medication.
6. Cardiac and chest examination.
7. Degree of HF acording to New York Heath Association (NYHA) classification.

Functional calssification defines four functional classes as:

- **Class I:** HF doesnt couse limitation to physical activity ordinary physical activity doesnot cause symptoms.
- **Class II:** HF cause slight limitation to physical activity,patients are comfortable at rest, but ordinary physical activity resulte in HF symptoms.
- **Class III:** HF cause marked limitation to physical activity, patients are comfortable at rest,but less than ordinary physical activity resulte in HFsymptoms.
- **Class 1V:** HF patients are unable to carry on any physical activity without HF symptom or have symptoms whene at rest [(9)].

The following investigations were performed to every patient .

1. Rest 12 leads ECG.
2. Echocardiology.
3. Laboratory investigation:
   - Complete blood count (CBC): It was done by automated cell counter (Symex XS-1000i, Japan).
   - Alanine aminotransferase (ALT) and aspartate aminotransferase (AST).
   - Serum urea and creatinine.
   - Fasting blood glucose, HBAlc.
   - Lipogram (total cholesterol, LDL-c, TG and HDL-cholesterol).

GFR was calculated by this equation: eGFR (mL/min/1.73m^2) = 186 (S.Cr in µmol/l × 0.011312) $^{-1.154}$ × (age)$^{-0.203}$ × (0.742 if female) × (1.212 if African/American Black) [(10)].

Ethical consent:

An approval of the study was obtained from Benha University Academic and Ethical Committee. Every patient signed an informed written consent for acceptance of participation in the study. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis

Data management and statistical analysis were done using SPSS version 25. (IBM, Armonk, New York, United States). Quantitative data were assessed for normality using Kolmogorov–Smirnov test and direct data visualization methods. Numerical data were summarized as means and standard deviations or medians and ranges. Categorical data were summarized as numbers and percentages. Quantitative data were compared according to HF using Student's t-test or Mann-Whitney U test for normally and non-normally distributed numerical variables, respectively. Categorical data were compared using the Chi-square test. All statistical tests were two-sided. P values $\leq$0.05 were considered significant.

RESULTS

This cross-sectional study was conducted on 200 patients with type 2 diabetes attending an outpatient and inpatient clinics of Benha teaching hospitals. The prevalence of HF in diabetic patients was 35.5% [28 (39.4%) females and 43 (60.6%) males], while patients without heart failure represented 64.5% [85 (65.9%) females and 44 (34.1%) males]. They were middle aged, with a mean age of 60 (SD 11) for patients with HF, and 58 (SD 11) for those without HF. BMI was significantly higher in those with HF (80.8%) than those without HF (70.1%), with p-value <0.001. Furthermore, waist circumference was significantly higher in those with HF (93%) than those without HF (84%), with p-value of 0.004. Table 1 compare clinical data of both groups.

Table (1): Comparison between patients with and without heart failure regarding socidemographic characteristics.

Variable		Heart failure		P-value
		Yes (n = 71)	No (n = 129)	
Age (years)	Mean ±SD	60 ±11	58 ±11	0.303
Gender	Males n (%)	43 (60.6)	85 (65.9)	0.453
	Females n (%)	28 (39.4)	44 (34.1)	
Residence	Rural n (%)	21 (29.6)	55 (42.6)	0.069
	Urban n (%)	50 (70.4)	74 (57.4)	
Duration of DM (years)	Median (range)	10 (4 - 23)	5 (2 - 16)	<0.001
BMI	Mean ±SD	29.6±9.6	25.3±5.7	0.001
Waist circumference (cm)	Mean ±SD	93 ±24	84 ±20	0.004
Systolic blood pressure (mmHg)	Mean ±SD	138 ±23	132 ±21	0.069
Diastolic blood pressure (mmHg)	Mean ±SD	84 ±13	81 ±14	0.126

Student's t-test was used for numerical data. Chi-square test was used for categorical data

Hemoglobin, Creatinine, Fasting blood glucose, HBA1c, mean triglycerides, mean LDL and mean cholesterol were significantly higher in those with HF failure than those without. GFR and mean HDL was significantly lower in those with HF than those without HF (Table 2).

Table (2): Comparison between patients with and without heart failure regarding laboratory tests

Variable		Heart failure		P-value
		Yes (n = 71)	No (n = 129)	
Hemoglobin (g/dl)	Mean ±SD	10.8 ±2.6	12.4 ±1.5	<0.001
ALT (units/L)	Mean ±SD	28 ±6	30 ±7	0.062
AST (units/L)	Mean ±SD	28 ±6	27 ±6	0.219
Creatinine (mg/dL)	Mean ±SD	1.61 ±0.24	1.13 ±0.29	<0.001
GFR (mL/min)	Mean ±SD	47 ±8	87 ±11	<0.001
Fasting blood glucose (mg/dL)	Mean ±SD	152 ±16	131 ±19	<0.001
HbA1C (%)	Mean ±SD	10.1 ±1.6	8.5 ±1.5	<0.001
Triglyceride (mg/dL)	Mean ±SD	278 ±60	220 ±7	<0.001
Total cholesterol (mg/dL)	Mean ±SD	312 ±47	295 ±54	0.023
HDL (mg/dL)	Mean ±SD	29 ±1	35 ±2	<0.001
LDL (mg/dL)	Mean ±SD	153 ±19	147 ±22	0.031

Student's t-test was used.

Number of patients with dysrhythmia, atrial fibrillation, atrial flutter, ventricular tachycardia, sinus tachycardia, sinus bradycardia, heart block was significantly higher in patients with HF than patients without HF. Number of patients with premature ventricular contractions and ST elevation was insignificantly different between patients with and without HF (Table 3).

Table (3): Dysrhythmia and ECG in patients with and without heart failure

Variable			Heart failure		P-value
			Yes (n = 71)	No (n = 129)	
Dysrhythmia		n (%)	69 (97.18%)	5 (3.88%)	**<0.001**
Tachycardia					
Sinus tachycardia		n (%)	16 (22.54%)	8 (6.20%)	**0.001**
Ectopic tachycardia	**Supraventricular**				
	Atrial fibrillation	n (%)	10 (14.08%)	2 (1.55%)	**<0.001**
	Atrial flutter	n (%)	4 (5.63%)	0 (0%)	**0.015**
	Ventricular				
	Ventricular tachycardia	n (%)	10 (14.08%)	0 (0%)	**<0.001**
	Premature ventricular contractions	n (%)	2 (2.82%)	0 (0%)	0.125
Bradycardia					
Sinus bradycardia		n (%)	10 (14.08%)	6 (4.65%)	**0.028**
Heart block		n (%)	13 (18.31%)	1 (0.7%)	**<0.001**

Chi-square test was used for categorical data. Echo parameters (PWt, , RV, aorta, and LA dimentions) were significantly higher in patients with HF than patients without HF. Echo parameters (LVEDD, LVESD, FS, and EF) were significantly lower in patients with HF than patients without HF (Table 4).

Table (4): Echo parameters in patients with and without heart failure

Variable		Heart failure		P-value
		Yes (n = 71)	No (n = 129)	
LVEDD (cm)	Mean ± SD Range	4.81 ± 0.53 4.32 – 6.87	4.96 ± 0.38 4.41 – 6.87	**0.036**
LVESD (cm)	Mean ± SD Range	2.94 ± 0.49 2.61 – 4.91	3.26 ± 0.25 2.67 – 4.91	**<0.001**
PWt (cm)	Mean ± SD Range	1.61 ± 0.78 0.75 – 4.74	0.85 ± 0.11 0.75 – 1.37	**<0.001**
FS (%)	Mean ± SD Range	24.36 ±2.19 18.2 –27.33	39.12 ± 3.97 20.63 – 43.73	**<0.001**
EF (%)	Mean ± SD Range	47.37 ±9.92 32 – 70	63.54 ± 4.94 35 – 70	**<0.001**
Rv	Mean ± SD Range	2.54 ± 0.20 2.29 – 3.1	2.31 ± 0.19 2.06 – 3.1	**<0.001**
Aorta/cm	Mean ± SD Rang	2.73 ± 0.84 2.58 – 2.95	2.64 ± 0.14 2.37 – 2.95	**<0.001**
LA/cm	Mean ± SD Range)	4.05 ± 0.18 3.41 – 4.2	3.64 ±0.19 3.36 – 4.18	**<0.001**

LVEDD: Left ventricular end-diastolic diameter, LVESD: Left ventricular end-systolic diameter, PWt: Posterior wall thickness, FS: Fractional shortening, EF: Ejection fraction, Rv: Right ventricle, LA: Left atrium, Independent t-test was used

The number of patients with HF who were on sulfonylurea and Thiazolidinediones (TZDs) was significantly higher than those without HF who were using them. The number of patients who were on insulin, biguanides, dpp4I, SGLT2I, and Alpha-glucosidase inhibitors was insignificantly different between patients with or without HF (Figure 1).

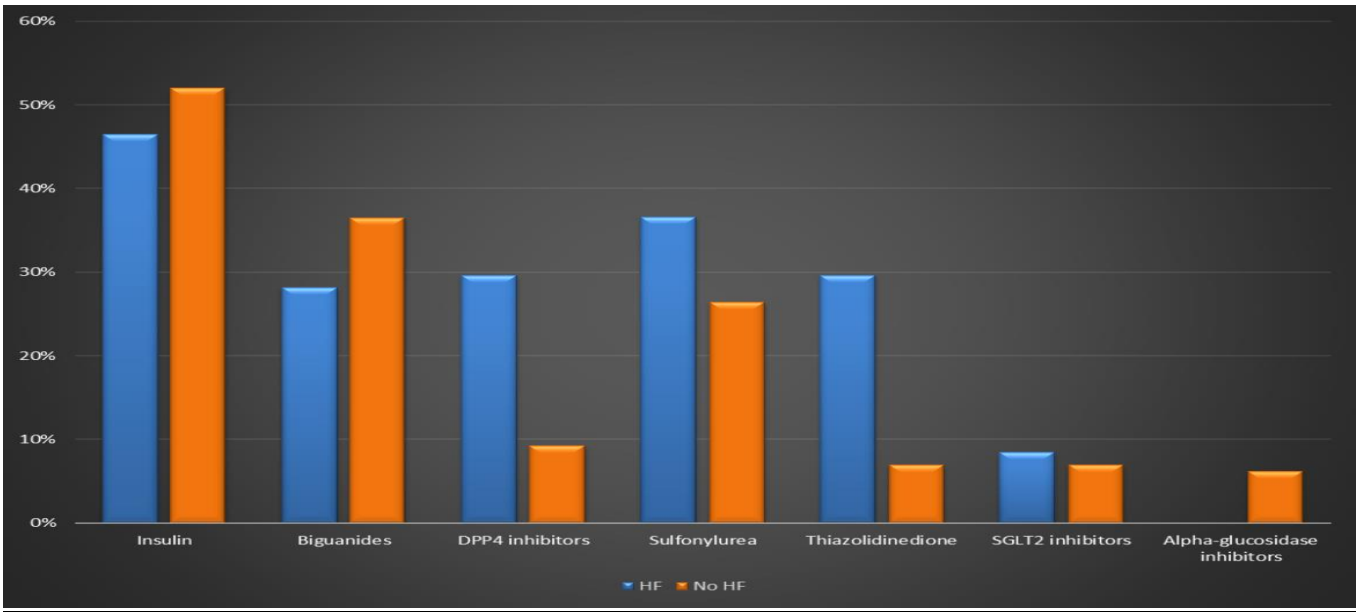

Figure (1): Oral hypoglycemic drugs use according to heart failure

DISCUSSION

In the current study the prevalence of HF in diabetic patients was 35.5% while patients without HF were 64.5% .

This is in agreement with Lehrke and Marx [11], A retrospective cohort study analyzed data from the Kaiser Permanente Northwest database of 8231 patients with DM, none of whom had HF at baseline, and 8845 matched subjects without DM; the follow-up period was up to 6 years. Incident HF was 30.9 per 1000 person-years in subjects with DM and 12.4 per 1000 person-years in subjects without DM.

This is in agreement with Nichols *et al.* [12], who established that HF was identified in 11.8% of diabetic patients.

DM is associated with hyperglycemia-specific microvascular complecation. Furthermore, macrovascular complications, especially coronary artery disease (CAD). **In this study** Regarding the ejection fraction in the studied patients, it was preserved in 28 (39.4%) patients while it was reduced in 43 (60.6%) patients.

This is in agreement with **Lehrke and Marx[11]** which found diabetic patients who had HF, 50% had (HFpEF) and 50% (HFrEF).

This can be explained by that many patients in our study may have metabolic syndrome (insulin resistance, obesity, atherogenic dyslipidemia and hypertension). Metabolic syndrome is usualy associated with increase risk factor of developing HF especialy heart failure with reduced EF.

In this study approximately one-third of the patients were hypertensive (33.5%). Ischemic heart disease was reported in 15.5%, and only 5% had cardiomyopathy.

Boonman-de Winter *et al.* [13] in cross-sectional study of 581 patients with DM in Netherlands,161 were found to have HF, 73.9% had hypertension and 31.1% of these patients had ischemic heart disease.

The development of HF in patients with type 2 DM is largely attributable to concomitant hypertension and coronary artery disease.

DM can cause cardiomyopathy in many mechanisms including effects of hyperglycemia, advanced glycation end products, autonomic dysfunction, microangiopathy, subclinical myocardial necrosis, mitochondrial dysfunction, lipotoxicity.

In this study the most frequent risk factors for developing HF were anemia in 129 (64.5%) cases, excess salt intake in 40 (20.0%) cases, non-compliance in 26 (13.0%) cases, thyrotoxicosis in 25 (12.5%) cases, physical and emotional stress in 23 (11.5%) cases and infection in 10 (5.0%).

This is in agreement with **Ezekowitz *et al.* [14]** which stated that anemia is a precipitating factor of HF and its presence is associated with disease severity and mortality.

Anemia can cause cardiac stress by increasing stroke volume and tachycardia. Anemia can also decrease blood flow to the kidney and subsequently fluid retention and increasing cardiac stress. Anemia may also occur as complication of HF which can be explained as the anemia of chronic illness. Many mechanisms , also involved such as hematinic deficiency, the direct effect of some drugs for example ACE inhibitors and cytokines, which may interfere with erythropoiesis.

In this study, Glycemic control was significantly lower in those with HF (9.9%) than those without (68.2%). P-value was less than 0.001. Fasting blood glucose and HBA1c were significantly higher in those with HF than those without. Unlike **Kenny and Abel[15]** and **Lehrke and Marx[11],** which showed that tight glycemic control doesn't reduce incidence of macro vascular complications.

Hyperglycemia, oxidant stress and inflammation are main risk factors that contribute in cardiovascular complications despite tight glycemic control; it can be explained that poor glycemic control or even transient episodes of hyperglycemia.

Worse the ability of endogenous vasoreparative systems that are mediated epigenetic changes in several cells (progenitor cells, stem cells, mononuclears, immune cells), which called “vascular glycemic memory” or “metabolic memory”.

So prior glucose control has sustained effects that persist even after return to more usual glycemic control.

In this study the number of patients with HF who were on TZDs was significantly higher than those without HF who were using it ($p<0.001$). This is in agreement with **Lehrke and Marx[11], Kenny and Abel[15] and Lago *et al.* [16].**

According to Lago *et al.* [16] 360 of 20191 patients who had either prediabetes or type 2 DM had HF (214 with TZDs and 146 with comparators). Results showed no heterogeneity of effects across studies ($I2=22.8\%$; p for interaction=0·26) which indicated a class effect for TZDs. Compared with controls, patients given TZDs had increased risk for development of congestive HF across a wide background of cardiac risk (relative risk 1.72, 95% CI 1.21–2.42, p=0.002). By contrast, the risk of cardiovascular death was not increased with either of the two TZDs (0.93, 0.67–1.29, p=0.68).

This is in agreement with Lehrke and Marx [11], stated that TZDs cause fluid retention which leads to HF TZDs are not recommended in patients with HF, and is contraindicated in patients with established NYHA III/IV HF.

This is in agreement with Kenny and Abel[15], The proactive trial suggested that pioglitazone was associated with 26.4% increase in edema compared with 15.1% for placebo. TZD-induced edema is linked to increased vascular permeability, vasodilation, and fluid

retention by the kidney. Activation of PPARs in the nephrons of the kidney by TZDs promotes the expression of epithelial sodium channels in the collecting duct which increases the retention of salt and water leading to fluid retention.

In this study, the number of patients with HF who were on sulfonylurea was significantly higher than those without HF who were using it ($p<0.001$). **This is in agreement with Lehrke and Marx [11],** Limited data exist about the use of sulfonylureas and HF incidence. No difference in HF events was recorded in the UKPDS trial comparing sulfonylureas treatment with dietary intervention in 3867 newly diagnosed patients with DM. Nevertheless, in a retrospective cohort study found that sulfonylurea treatment to be associated with increased HF risk when compared with metformin. **This is in agreement with Kenny and Abel [15]**, although some studies have suggested a relation between 1st generation SUs and cardiovascular mortality, to date there is no cardiovascular studies that has evaluated cardiovascular safety of SU, So there is controversy about the effects of SU on cardiovascular outcome .

In this study,the number of patients who were on SGLT2I was insignificantly different between patients with and without HF.

Many studies refer to importance of SGLT2I drugs in treatment of diabetic patient with HF **Lehrke and Marx [11], Kenny and Abel [15], Hallow *et al.* [17], Malik *et al.* [18].**

Hallow *et al.*[16], stated that using SGLT2I decrease HF complication in the EMPA-REG OUTCOMES trial by reducing reabsorption of both sodium and glucose in a 1:1M ratio causing osmotic diuresis and electrolyte-free water clearance, leading to a greater clearance of fluid from the IF space, so congestion is reduced and early reduction of HF complications. So, it hypothesize that using SGLT2I is better in reducing congestion in HF patients than traditional diuretics.

This is in agreement with Lehrke and Marx[11], Empagliflozin Cardiovascular Outcome Event Trial in Type 2 DM Patients–Removing Excess Glucose (EMPA-REG OUTCOME). The study was on7020 diabetic patients with HF showed a significant 14% relative risk reduction in the primary endpoint of cardiovascular death, myocardial infarction, and stroke; a significant 38% relative risk reduction in cardiovascular death; as well as a significant 32% relative risk reduction in overall mortality

Kenny and Abell[15] and Malik *et al.* [18], both confirm the role of SGLT2I in reduction of cardiovascular complection in type 2 diabetes.

In this study, The number of patients who were on DPP-4 inhibitors was insignificantly different between patients with or without HF. **This is inagreement with Lehrke and Marx[11]**, the DPP-4 inhibitors increase the bioavailability of the incretin hormones glucagon-like peptide 1 (GLP-1) and gastric inhibitory polypeptide, leading to glucose-dependent insulin secretion.

Three cardiovascular safety trials have been reported for the DPP-4 inhibitors saxagliptin (Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–Thrombolysis in Myocardial Infarction [SAVOR-TIMI).

In our study, The number of patients who were on biguanides was insignificantly different between patients with or without HF.

This is inagreement with Kenny and Abell[15], Metformin is the most widely used oral anti-diabetic drugs and it is the first line therapy in type 2 DM because of its high safety profile. It is both safe and efficacious both as monotherapy and in combination with other anti-diabetic drugs and insulin. The UKPDS stated that patients with type 2 DM on metformin had 36% reduced risk of all-cause mortality and 39% lower risk of MI compared with type 2 diabetic patients treated otherwise. Other more recent analysis has supported the case for metformin having a survival benefit in diabetic patients with HF compared with alternative glucose-lowering regimens.7 Metformin was associated with better short-term and long-term prognosis than any other antidiabetic treatment in patients with acute coronary syndrome and HF.

Study limitations: The small sample number of patients as they were recruited from one area, Benha Teaching Hospitals and also not all drugs was involved like GLP-1 RAs.

CONCLUSION

The pathophysiology of HF in DM is complex and represents a cardiovascular complication of DM that contributes importantly to morbidity and mortality. Different classes of antidiabetic drugs may have divergent effects on HF, and that some classes of agents might actually reduce HF risk. There is also a strong relation between exogenous insulin use and both prevalent and incident CHF. TZDs are not recommended in patients with symptomatic HF, and initiation of therapy is contraindicated in patients with established NYHA III/IV HF. The DPP-4 inhibitors have cardiovascular safety in high-risk populations of diabetic patients. The SGLT2 inhibitors have beneficial cardiovascular outcome.

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