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Clinical profile of diabetic patients with heart failure admitted in tertiary care teaching hospital, Kishanganj, Bihar- An Observational Study

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Abstract
Background: *Diabetes mellitus and heart failure are two multifaceted entities characterised by high morbidity and mortality. Early epidemiological and prospective studies have observed the frequent co-existence of both conditions.*
Methodology: *An echocardiography was done and investigations like complete haemogram, HbA1C, FBS, PPBS, renal profile and fasting lipid profile was also done. Echocardiography was done by Siemens CV70 machine in department of cardiology and HbA1C was measured by High Pressure Liquid Chromatographic method in department of biochemistry.*
Results: *A total of 100 patients coming with signs and symptoms of HF who are also diabetic were selected for the study, in whom 72 were male and 28 were female. Predominant symptoms were shortness of breath (100%) followed by swelling of legs (48%) and palpitation (29%). History suggestive of paroxysmal nocturnal dyspnea was present in 27 (27%) patients. Atrial fibrillation was observed in 23% cases. LVEF [<50%] was recorded 62% cases at presentation. Mean HbA1C was 7.3±0.9. Anaemia was reported about 31% cases. Dyslipidemia was noticed about 47% of the study participants with diabetes with heart failure. Among 100 patients 62 (62%) presented with left ventricular ejection fraction <50% and 38 (38%) presented with left ventricular ejection fraction ≥50%.*
Conclusion: *Diabetes is an independent risk factor for the development of congestive heart failure and heart failure patients with diabetes have a worse prognosis than those without diabetes.*
Keywords: *Diabetes mellitus, Heart failure, Clinical Profile, Left ventricular ejection fraction.*

Introduction

Diabetes mellitus (DM) is a group of diseases characterised by metabolic disturbances with increasing prevalence worldwide.[1] Individuals with DM present several detrimental micro- and macrovascular complications such as retinopathy, nephropathy, neuropathy, atherosclerosis and coronary heart disease.[2,3] Heart failure (HF) is a syndrome with a complex pathophysiology, several aetiologies and different clinical presentations characterised by high morbidity and mortality.[4] According to some reports the co-existence of HF and DM is as high as almost 40 %[5], growing the necessity for more in-depth understanding of the common pathophysiological pathways and for effective management of both entities.[6]

Type 2 diabetes and heart failure are common companions in clinical practice. Between 20% and 40% of all patients with heart failure has diabetes.[7] This is partly because all the major risk factors for heart failure also cluster in patients with type 2 diabetes, including obesity, hypertension, advanced age, sleep apnoea, dyslipidaemia, anaemia, chronic kidney disease (CKD), and coronary heart disease (CHD). Diabetes itself independently contributes to the development and progression of heart failure.[8] There is strong epidemiological evidence linking poor glycaemic control and the risk of heart failure. For example, in patients with type 1 diabetes from the Swedish National Diabetes Registry the incidence of heart failure increased linearly with HbA1c, and remained significant after adjustment for age, sex, duration of diabetes, cardiovascular risk factors, and baseline or intervening acute myocardial infarction and other co-morbidities.[9] Similarly, in a number of prospective observational studies in type 2 diabetes there is a consistent linear relationship between glycaemic control and heart failure, such that overall adjusted risk ratio (RR) for CHF was 1.15 [95% confidence interval (CI) 1.10-1.21] for each percentage point higher HbA1c.[10]

Heart failure is a clinical diagnosis.[11] An ejection fraction (EF) of <50% in a patient with heart failure symptoms is termed heart failure with reduced ejection fraction (HFrEF), and an EF of ≥50% in a patient with heart failure symptoms is termed heart failure with preserved EF (HFpEF).[12] Diabetes mellitus, and in particular the type 2[13], has progressively become more common. Factors increasing the prevalence include an ageing population, an increasing body mass and decreased demands of physical activity.[14] Accordingly, efforts for early diagnosis and appropriate management are of ultimate importance. In diabetic patients, the existence of a pre-clinical diastolic dysfunction has been well defined and estimates of prevalence vary from 20% to 60% depending on the Doppler echocardiographic criteria that was used to define diastolic dysfunction.[15] Unfortunately, there have been few population-based studies to evaluate the outcomes of pre-clinical diastolic dysfunction in diabetic patients. As such similar clinical published data is lacking in patients of diabetes with heart failure in the Eastern part of India. This study was designed to evaluate the clinical presentation of patients with heart failure who are also diabetic. Demographical parameters, risk factors, NYHA Class at presentation, systemic examination findings, HbA1C level, echocardiography features and other relevant parameters were studied.

Materials and Methods

This cross sectional, non-interventional observational study was conducted with patients in the Diabetic and Cardiology OPD of a tertiary care teaching hospital in Eastern India from January 2016 to December 2016. Hundred patients satisfying the diagnostic criteria for diabetes and heart failure who fulfill inclusion criteria were taken.

Inclusion Criteria

- Male and female patients admitted with heart failure and established type 2 diabetes mellitus

- Age ≥ 18 years
- Patients willing to give written informed consent for the study.

Exclusion Criteria

- Age < 18 years
- Pregnancy
- Unwilling or unable to comply with protocol

A written informed consent was taken from them. An echocardiography was done and investigations like complete haemogram, HbA1C, FBS, PPBS, renal profile and fasting lipid profile was also done. Echocardiography was done by Siemens CV70 machine in department of cardiology and HbA1C was measured by High Pressure Liquid Chromatographic method in department of biochemistry.

Results

A total of 100 patients coming with signs and symptoms of HF who are also diabetic were selected for the study, in whom 72 were male and 28 were female. Patients were from all age groups. Youngest was of 27 yrs age and oldest was 89 years age. Maximum numbers of patients were in age group of 51-60 years (43%) followed by those in 41- 50 years (23%) and 61-70 years (19%) age groups respectively. None of the case was reported between 18-20 years. Mean age was 52.7±19.8yrs [Table 1].

Table 1: Demographic characteristics of diabetic and heart failure patients [n=100]

Characteristics	No. of patients	Percentage/ Mean±SD
Males	72	72%
Females	28	28%
Mean age [years]	100	52.7±19.8
Age groups [years]		
< 20	0	0
21-30	1	1%
31-40	3	3%
41-50	23	23%
51-60	43	43%
61-70	19	19%
71-80	8	8%
>80 years	3	3%
Mean body mass index	100	26.8±3.5

Table 2: Clinical characteristics of diabetic and heart failure patients [n=100]

Characteristics	No. of patients	Percentage
Shortness of breath	100	100%
Swelling of legs	48	48%
Palpitation	29	29%
Ascites	9	9%
Paroxysmal nocturnal dyspnea	27	27%
NYHA Class		
1	12	12%
2	24	24%
3	42	42%
4	22	22%
Medication History		
Oral antidiabetic agents	67	67%
Only insulin therapy	14	14%
Both	19	19%
Diuretics	56	56%
ACE inhibitors/ ARBs	79	79%
Beta blockers	37	37%
Digoxin	28	28%
Antiplatelets	30	30%
Statins	41	41%
Undergone CABG/PTCA for CAD	7	7%
Smokers	39	39%
Alcoholic	28	28%
Duration of Diabetes		
<1 yr	3	3%
1-5 yrs	29	29%
5-10 yrs	41	41%
>10 yrs	27	27%

Predominant symptoms were shortness of breath (100%) followed by swelling of legs (48%) and palpitation (29%). History suggestive of paroxysmal nocturnal dyspnea was present in 27 (27%) patients [Table 2]. Patient's functional class was assessed on admission and majority presented in NYHA class 3 (42%) and class 2 (24%). There was good number cases presented with NYHA class 4 (22%) [Table 2]. Medication history revealed that 67% was on oral hypoglycemic drugs, 14% on insulin and 19% was on both. History of medications revealed that other than antidiabetic; medications like diuretics 56%, ACE inhibitors/ARBs 79%, beta blockers 37%, digoxin 28%, antiplatelet agents 30% and statins 41% patients. About 39% were smoker and 28% used to take alcohol [Table 2]. Duration of diabetes among patients was 3% less than 1 yr, 29% (1-5 yrs), 41% (5-10 yrs) and 27% (>10 yrs). On examination jugular venous pressure was elevated in 57% patients, most of them had tachycardia. S3 was present in 38% patients and S4 was there in 29% patients. Edema was present in 48%patients.

Table 3: Duration of diabetes mellitus and NYHA class relation

Duration of Diabetes	NYHA Class 1	NYHA Class 2	NYHA Class 3	NYHA Class 4
< 1yr	2	1	0	0
1- 5 yrs	6	10	7	6
5-10 yrs	3	8	21	9
>10 yrs	1	5	14	12

NYHA Class 3 heart failure was much common in the age group of 5-10 yrs followed by >10 yrs. NYHA Class 4 heart failure was much common in the age group of >10 yrs followed by 5-10 yrs [Table 3]. NYHA Class 2 was much more common in the age group of 1- 5 yrs followed by 5-10 yrs.

Table 4: Laboratory and clinical parameters in the study subjects [n=100]

Characteristics	No. of patients	Percentage
Systolic BP, mmHg	100	137 ± 28.5
Diastolic BP, mmHg	100	85 ± 19.7
Hypertension	58	58%
Rhythm at admission		
Atrial fibrillation	23	23%
Paced rhythm	7	7%
Dyslipidemia	47	47%
Raised triglycerides	35	74.5%
Raised LDL	27	57.4%
Reduced HDL	33	70.2%
Hb	100	11.7 ± 3.2
Anemia	31	31%
Hyponatremia	23	23%
Hypokalemia	11	11%
Albumin	100	3.65 ± 0.7
FBS	-	138.8± 21.7
PPBS	-	213± 29.7
HbA1C	-	7.3±0.9
BUN, mg/dL [blood urea nitrogen]	-	43.8 ± 17.9
Creatinine, mg/dL	-	1.98 ± 1.19
BUN/Cr ratio	-	25.5 ± 11.7
Echocardiographic findings		
LVEF, % [left ventricular ejection fraction]	-	42 ± 15
LVEF, %<50%	62	62%
LVEF, %>50%	38	38%

Atrial fibrillation was observed in 23% cases. LVEF [<50%] was recorded 62% cases at presentation. Mean HbA1C was 7.3±0.9. Anaemia was reported about 31% cases. Dyslipidemia was noticed about 47% of the study participants with diabetes with heart failure [Table 4]

Table 5: HbA1C level relation with NYHA class

HbA1C Level	Class 1	Class 2	Class 3	Class 4
5- 6%	2	1	2	0
6.1- 7%	7	5	13	3
7.1- 8%	3	8	18	7
8.1- 9%	0	6	7	7
>9%	0	4	2	5

Among 100 patients 62 (62%) presented with left ventricular ejection fraction <50% and 38 (38%) presented with left ventricular ejection fraction ≥50%. Average LVEF was 42 ± 15, septal thickness 11.4±1.9 and posterior wall thickness was 10.5±1.4. NYHA Class 3 was more [18%] in the HbA1C group7.1- 8% [Table 5]

Table 6: Duration of diabetes mellitus and LVEF relation

Duration of diabetes	LVEF <30%	LVEF-31-40%	LVEF-41-50%	LVEF->50%
< 1 yr	0	1	2	22
1-5 yr	1	5	11	9
5-10 yr	3	9	15	5
>10yr	7	5	3	2

A correlation was tried to achieve between duration of diabetes and left ventricular ejection fraction. About 22 (22%) patients of diabetes duration < 1 yr had LVEF ≥50%. Thus longer the duration of diabetes, more it is likely to present with heart failure with preserved ejection fraction [Table 6].

Table 7: Diastolic dysfunction in study participants

Grade of diastolic dysfunction	No of patients
Grade 1	8
Grade 2	22
Grade 3	35
Grade 4	17

Diastolic dysfunction was present more commonly in grade 3 category (35%). Systolic dysfunction is present more commonly in diabetic patients with duration more than 10 yrs [Table 7].

Discussion

The present study was aimed to record the clinical profile of the patients with heart failure and diabetes mellitus with regards to history, investigations, risk factors and echocardiography. The study was also done to know the prevalence of systolic and diastolic dysfunction among population, and to correlate HbA1C level with NYHA class at presentation with echocardiographic evaluation of Left ventricular diastolic function. The Framingham study was the first epidemiological study estimated increase in the incidences of heart failure for young diabetic males and females by fourfold and eightfold, respectively.[16]

Present study demonstrated diastolic dysfunction was common in patients with DM. The existence of a pre-clinical diastolic dysfunction has been well defined in diabetic patients and estimates of prevalence found to be vary from 20% to 60% depending on the doppler echocardiographic criteria. Study also revealed that LV diastolic dysfunction may precede LV systolic dysfunction in diabetic patients. The possible mechanisms for early restrictive disease in diabetic patients is likely due to microangiopathy, interstitial fibrosis, extracellular collagen deposition, calcium transport abnormalities, and neurohormonal alterations, alone or in combination.[17, 18] Patil MB et al also showed that diastolic dysfunction was present in 64% of the patients. Diastolic dysfunction was more common among female sex (68.18%) compared to male (60.17%). Diastolic dysfunction was significantly associated with uncontrolled diabetes as assessed by HbA1c levels. Diastolic dysfunction was more common in patients who were on treatment with both oral hypoglycemic agents and insulin. The prevalence of diastolic dysfunction increased with duration of diabetes. Study also revealed a linear progression of diastolic dysfunction with the increase age.[19]

In present study 100 diabetic patients with heart failure were included and there was male predominance (72%), with increased prevalence

during 51-60 yrs. age groups. The proportion of subjects with diabetes in CONSENSUS (Cooperative North Scandinavian Enalapril Survival Study)[20], SOLVD (Studies of Left Ventricular Dysfunction)[21], V-HeFT II (Vasodilator Heart Failure Trial II)[22] and ATLAS (Assessment of Treatment with Lisinopril and Survival)[23] was 23%, 25%, 20% and 20% respectively.

Predominant symptoms were shortness of breath (100%) followed by swelling of legs (48%) and palpitation (29%). History suggestive of paroxysmal nocturnal dyspnea was present in 27 (27%) patients [Table 2]. Patient's functional class was assessed on admission and majority presented in NYHA class 3 (42%) and class 2 (24%). There was good number cases presented with NYHA class 4 (22%) [Table 2]. Medication history revealed that 67% was on oral hypoglycemic drugs, 14% on insulin and 19% was on both. History of medications revealed that other medications were like diuretics 56%, ACE inhibitors/ARBs 79%, beta blockers 37%, digoxin 28%, antiplatelet agents 30% and statins 41% patients. About 39% were smoker and 28% used to take alcohol [Table 2]. Duration of diabetes among patients was 3% less than 1 yr, 29% (1-5 yrs), 41% (5-10 yrs) and 27% (>10 yrs).

On examination jugular venous pressure was elevated in 57% patients, most of them had tachycardia. S3 was present in 38% patients and S4 was there in 29% patients. Edema was present in 48%patients. Elevated jugular venous pressure is a manifestation of abnormal right heart dynamics, mostly commonly reflecting elevated pulmonary capillary wedge pressure from left heart failure. This usually implies fluid overload, indicating the need for diuresis.

HbA1C was elevated in most of the patients and HbA1C level had a significant relationship with diastolic dysfunction grade but not so significant relation with LVEF or NYHA class. The relationship between adverse outcomes and HbA1c in patients with both diabetes and HF appears U-shaped, with the lowest risk of death in those patients with modestly impaired glucose control (HbA1c 7.0-7.8%) and an increased risk of mortality with higher or lower HbA1c levels.[24] The present study significantly correlated with elevated HbA1C and elevated FBS to LVDD, whereas age and gender has no statistical significance.

The SOLVD study revealed that diabetes was an independent predictor of morbidity and mortality both in symptomatic and asymptomatic heart failure.[25] This relationship was confirmed by the RESOLVD trial.[26] Different study showed that diabetic patients experience a higher incidence of heart failure and increased mortality after acute myocardial infarction than nondiabetic patients.[27, 28, 29]

HF is an independent risk factor for the development of DM. During a 3-year follow-up 29% of HF patients without DM were shown to develop DM compared with 18% of matched control subjects.[30] Another study revealed that 33% of all HF patients have concomitant DM and this number rises up to 40% in patients admitted with acute decompensated HF.[31] Sarma S et al[32] showed approximately 40% of hospitalized HF patients with low EF have DM. DM in hospitalized patients is associated with worse prognosis[32], increased risk for combined CV mortality and HF-related hospitalization[33], and longer hospital stay[31], despite receiving care that is similar to that for patients without DM[34] although this paradigm is not a consistent finding.

Anaemia is also a common companion to diabetes and this is because of the high prevalence of chronic kidney disease in patients with diabetes, leading to functional erythropoietin deficiency.[35, 36] Patients with heart failure and anaemia generally experience more severe symptoms. They may have higher rates of hospitalization and reduced survival when compared with patients without anaemia.[37] Elevated body mass is causally linked to both diabetes and incident heart failure. The greater the elevation in body weight, the greater the risks and the worse the clinical

outcomes.[38] Obesity triggers to concentric left ventricular hypertrophy.[35]

Insulin resistance and hyperglycemia may accompany type 2 DM. Several adaptive and maladaptive cellular responses may lead to specific changes in myocardial structure and function (diabetic cardiomyopathy). Longstanding metabolic and functional alterations ultimately lead to irreversible structural changes. Comorbidities seen commonly in patients with DM, such as hypertension, dyslipidemia, microvascular dysfunction, autonomic dysfunction, and renal impairment may accelerate the progression of cardiac dysfunction toward advanced disease.[39] Boyer *et al*.[40] revealed that the prevalence of LV diastolic dysfunction in asymptomatic, normotensive patients with type 2 diabetes disease is high and about 75% subjects. They revealed that TDI detected diastolic dysfunction more often than any other echocardiographic parameter. In present study, the prevalence of diastolic dysfunction was 54.33%. Poulsen *et al*.[41] in their prospective observational study of 305 patients with type 2 DM showed that abnormal LV filling is closely associated with abnormal myocardial perfusion on myocardial perfusion scintigraphy.

In the present study we found that BUN was 43.8 ± 17.9. Elevated BUN levels can predict renal hypoperfusion and may be due to low cardiac output or renal venous congestion secondary to HF. Under conditions of reduced renal perfusion such as dehydration or low cardiac output, a complex neurohormonal mechanism is activated, which stimulates the release of vasopressin and activates the renal sympathetic nervous system and RAAS, all of which contribute to a disproportionate reabsorption of urea.[42, 43]

Conclusion

HF and DM are common clinical entities that frequently coexist in an individual patient. Two multifaceted entities characterized by high morbidity and mortality. Early epidemiological and prospective studies have observed the frequent co-existence of both conditions. The present study significantly correlated with elevated HbA1C and elevated FBS to LVDD, whereas age and gender has no statistical significance. The implication is that more aggressive metabolic care at an early stage of the disease may delay restructuring of the myocardium.

References

1. Guariguata L, Whiting DR, Hambleton I, et al., Global estimates of diabetes prevalence for 2013 and projections for 2035, Diabetes Res Clin Pract, 2014;103:137–49.
2. Tousoulis D, Papageorgiou N, Androulakis E, et al., Diabetes mellitus-associated vascular impairment: novel circulating biomarkers and therapeutic approaches, J Am Coll Cardiol, 2013;62:667–76.
3. Barber SR, Davies MJ, Khunti K, Gray LJ, Risk assessment tools for detecting those with pre-diabetes: A systematic review, Diabetes Res Clin Pract, 2014;105(1):1–13.
4. McMurray JJ, Adamopoulos S, Anker SD, et al., ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC, Eur Heart J, 2012; 33:1787–847.
5. Vasiliadis I, Kolovou G, Kolovou V, et al. Gene polymorphisms and thyroid function in patients with heart failure, Endocrine, 2014;45:46–54.
6. Dimitris Tousoulis, Evangelos Oikonomou, Gerasimos Siasos, Christodoulos Stefanadis. Diabetes Mellitus and Heart Failure. European Cardiology Review 2014;9(1):37–42.
7. McAlister FA, Teo KK, Taher M, et al. Insights into the contemporary epidemiology and outpatient management of congestive

heart failure. Am. Heart J. 1999; 138(1 Pt 1):87–94.
8. Thomas MC. Type 2 Diabetes and Heart Failure: Challenges and Solutions. Curr Cardiol Rev. 2016 Aug; 12(3): 249–255.
9. Lind M, Bounias I, Olsson M, et al. Glycaemic control and incidence of heart failure in 20,985 patients with type 1 diabetes: an observational study. Lancet. 2011; 378(9786):140–146.
10. Erqou S, Lee CT, Suffoletto M, et al. Association between glycated haemoglobin and the risk of congestive heart failure in diabetes mellitus: systematic review and meta-analysis. Eur. J. Heart Fail. 2013; 15(2):185–193.
11. McKee PA, Castelli WP, McNamara PM, Kannel WB. The natural history of congestive heart failure: the Framingham study. N Engl J Med. 1971;285:1441–6.
12. Bursi F, Weston SA, Redfield MM, et al. Systolic and diastolic heart failure in the community. JAMA. 2006; 296:2209–16.
13. American Diabetes Association: Report of the expert committee on the diagnosis and classification of diabetes mellitus. Diabetes Care 1997; 20: 1183–97.
14. Clark CM, Perry RC. Type 2 diabetes and macro vascular disease. Epidemiology and etiology. Am Heart J 1999; 138: 330–3
15. Wan S-H, Vogel MW, Chen HH. Preclinical Diastolic Dysfunction. Journal of the American College of Cardiology. 2014;63(5): 407-416.
16. Kannel WB, McGee DL. Diabetes and cardiovascular disease. The Framingham study. J Am Med Assoc 1979; 214: 2035–8.
17. Tsujino T, Kawasaki D, Masuyama T. Left ventricular diastolic dysfunction in diabetic patients: pathophysiology and therapeutic implications. Am J Cardiovasc Drugs. 2006; 6(4):219-30.
18. From AM, Scott CG, Chen HH. The Development of Heart Failure in Patients with Diabetes Mellitus and Preclinical Diastolic Dysfunction: A Population Based Study Journal of the American College of Cardiology. 2010;55(4):10.1016/j.jacc.2009.12.003.
19. Patil MB, Burji NP. Echocardiographic evaluation of diastolic dysfunction in asymptomatic type 2 diabetes mellitus. J Assoc Physicians India. 2012 May; 60:23-6.
20. The CONSENSUS trial study group. Effect of enalapril on mortality in severe congestive heart failure. N Engl J Med 1987; 316: 1429–35.
21. The SOLVD investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fraction and congestive heart failure. N Engl J Med 1991; 325: 293–302.
22. Cohn JN, Johnson G, Ziesche S et al. A comparison of enalapril with hydralazine-isosorbide dinitrate in the treatment of chronic congestive heart failure. N Engl J Med 1991; 325: 303–10.
23. Packer M, Poole-Wilson PA, Armstrong PW et al. on behalf of the ATLAS Study Group. Comparative effects of low doses and high doses of the angiotensin converting enzyme inhibitor lisinopril on morbidity and mortality in chronic heart failure. Submitted, 1998.
24. Aguilar D, Bozkurt B, Ramasubbu K, et al. Relationship of hemoglobin A1C and mortality in heart failure patients with diabetes. J. Am. Coll. Cardiol. 2009;54 (5):422–428.
25. Schindler DM, Kostis JB, Yusuf S et al. for the SOLVD investigators. Diabetes mellitus: a predictor of morbidity and mortality in the studies of left ventricular dysfunction (SOLVD) trials and registry. Am J Cardiol 1996; 77: 1017–20.
26. Suskin N, McKelvie RS, Roteaus J, Sigouin C, Wiece KE, Yususf S. Increased insulin and glucose levels in heart failure. J Am Coll Cardiol 1998; 3 (Suppl): 249A.
27. Gwilt DJ, Petri M, Lewis PW, Nattrass M, Pentecost BL. Myocardial infarct size and

mortality in diabetic patients. Br Heart J 1985; 54: 466–72.
28. Singer DE, Moulton AW, Nathan DM. Diabetic myocardial infarction. Interaction of diabetes with other preinfarction risk factors. Diabetes 1989; 38: 350–7.
29. Melchior T, Gadsboll P, Hildebrandt P, Kober L, Torp-Pedersen C. Clinical characteristics, left and right ventricular ejection fraction, and longterm prognosis in patients with non-insulin-dependent diabetes surviving and acute myocardial infarction. Diabetic Med 1996; 13: 450–6.
30. Amato L, Paolisso G, Cacciatore F, et al. Congestive heart failure predicts the development of non-insulin-dependent diabetes mellitus in the elderly: the Osservatorio Geriatrico Regione Campania Group. *Diabetes Metab*. 1997;23:213- 218.
31. Greenberg BH, Abraham Wt, Albert NM, et al. Influence of diabetes on characteristics and outcomes in patients hospitalized with heart failure: a report from the Organized Program to Initiate Lifesaving treatment in Hospitalized Patients with Heart Failure (OPtIMIZE-HF). *Am Heart J*. 2007;154: 277.e1-e8.
32. Sarma S, Mentz RJ, Kwasny MJ, et al. Association between diabetes mellitus and post-discharge outcomes in patients hospitalized with heart failure: findings from the EVEREST trial. Eur J Heart Fail 2013;15:194–202.
33. Nieminen MS, Brutsaert D, Dickstein K, et al. EuroHeart Failure Survey II (EHFS II): a survey on hospitalized acute heart failure patients: description of population. Eur Heart J 2006;27:2725–36.
34. Kapoor JR, Fonarow GC, Zhao X, Kapoor R, Hernandez AF, Heidenreich PA. Diabetes, quality of care, and in-hospital outcomes in patients hospitalized with heart failure. Am Heart J 2011; 162:480–486.e3.
35. Thomas MC. Anemia in diabetes: marker or mediator of microvascular disease? Nat. Clin. Pract. Nephrol. 2007;3(1):20–30.
36. Glogner S., Rosengren A., Olsson M., et al. The association between BMI and hospitalization for heart failure in 83,021 persons with Type 2 diabetes: a population-based study from the Swedish National Diabetes Registry. Diabet. Med. 2014;31 (5):586–594.
37. Anand I, McMurray JJ, Whitmore J, et al. Anemia and its relationship to clinical outcome in heart failure. Circulation. 2004;110(2):149–154.
38. Glogner S., Rosengren A., Olsson M., et al. The association between BMI and hospitalization for heart failure in 83,021 persons with Type 2 diabetes: a population-based study from the Swedish National Diabetes Registry. Diabet. Med. 2014;31(5):586–594.
39. Dei Cas et al. Impact of Diabetes on Epidemiology, Treatment, and Outcomes of Patients With Heart Failure. JACC: HEART FAILURE 2015 February; 3(2):136-45.
40. Boyer JK, Thanigaraj S, Schechtman KB, Pérez JE. Prevalence of ventricular diastolic dysfunction in asymptomatic, normotensive patients with diabetes mellitus. Am J Cardiol. 2004;93:870–875.
41. Poulsen MK, Henriksen JE, Dahl J, Johansen A, Gerke O, Vach W, et al. Left ventricular diastolic function in Type 2 diabetes mellitus: Prevalence and association with myocardial and vascular disease. Circ Cardiovasc Imaging. 2010;3:24–31.
42. Jujo K, Minami Y, Haruki S, et al. Persistent high blood urea nitrogen level is associated with increased risk of cardiovascular events in patients with acute heart failure. Esc Heart Failure. 2017;4(4):545-553.
43. Cowley AW Jr. Role of the renal medulla in volume and arterial pressure regulation. Am J Phys 1997; 273: R1–15.