Section A -Research paper
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Study of biochemical parameters and diabetic state on mortality and morbidity due to cardiac failure in type 2 diabetic patients

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Abstract
Background: Diabetic patients are at higher risk for development of heart failure, as diabetic state can lead to systolic heart failure as a result of macro vascular complications. Present study was aimed to study biochemical parameters and diabetic state on mortality and morbidity due to cardiac failure in type 2 diabetic patients at a tertiary hospital. **Material and Methods:** Present study was hospital based, observational, analytical study, 50 consecutive cases of heart failure with type 2 diabetes (diabetic group) and 50 consecutive cases with heart failure without diabetes (non-diabetic group) were studied. **Results:** Mean age, gender of patients were comparable in both groups. 37 (74%) patients from diabetic group and 21 (42%) patients from non-diabetic group were obese/over-weight, difference was statistically significant (p- 0.002). On 2D Echo, affected systolic function such as ejection fraction (<20 %, 20-35 % & 35-45 %) were comparable in both groups. & difference was not significant statistically ($p > 0.05$). 38 patients (76%) in diabetic group and 23 patients (46%) in non-diabetic group presented with evidence of affected diastolic function on 2D Echo , difference was statistically significant (p- 0.01). Mean triglyceride level, mean cholesterol level, mean serum urea level & mean serum creatinine level in diabetic group was more than from non-diabetic group, difference was statistically significant ($p < 0.05$). Patients had significantly higher length of hospital stay with higher HbA1c subgroups. 8 patients (16%) in diabetic group and 3 patients (6%) in non-diabetic group died & difference was not significant statistically ($p > 0.05$). **Conclusion:** Diabetic heart failure patients have a significantly higher likelihood to present with existence of diastolic dysfunction, significantly longer duration of hospital stay and also had a higher chance of death during stay.
Keywords: type 2 diabetes mellites, heart failure, obese/overweight, dyslipidemia

Introduction: Diabetes mellitus and heart failure are common comorbidities, and their prevalence has increased significantly. Amongst total diabetics 85% to 90% cases are of type 2 diabetes, there is explosive increase in type 2 diabetes in developing countries.[1,2] These are chronic conditions that frequently present in the same patient. Diabetic patients are at higher risk for development of heart failure, as diabetic state can lead to systolic heart failure as a result of macro vascular complications leading to myocardial infarctions at the same time they are also at increased risk for developing Diastolic Dysfunction as a result of microvascular changes.[3]

Heart failure patients with diabetes have a worse prognosis than non-diabetic heart failure patients. Study Of Left Ventricular Dysfunction (SOLVED) Study stated that diabetes is an independent predictor of morbidity and mortality both in symptomatic and non-symptomatic heart failure,[4] and this relationship was confirmed by randomized evaluation of strategies for Left Ventricular Dysfunctions Pilot Trial (RESOLVED).[5]

The presence of diabetes substantially accelerates development of heart failure in patients with myocardial infarction,[6,7] hypertension,[8] or atrial fibrillation,[9] leading to poorer prognosis. Diabetes predicts poor prognosis independently of coronary artery disease and level of Left Ventricular Ejection Fraction (LVEF)in heart failure patients.[10] Present study was aimed to study biochemical parameters and diabetic state on mortality and morbidity due to cardiac failure in type 2 diabetic patients at a tertiary hospital.

Material And Methods

Present study was hospital based, observational, analytical study, conducted in Department of Biochemistry, Dr. Shankarrao Chavhan Government Medical College, Vishnupuri, Nanded, India. Study duration was of 2 years (July 2013 to June 2015). Study approval was obtained from institutional ethical committee.

Inclusion criteria

- Patients of age > 18 years, either gender, admitted with heart failure in medicine wards & in ICU, willing to participate in present study

Exclusion criteria

- Heart failure with type 1 and types of DM (diabetes mellitus) other than type 2.
- In patients in whom written consent can not be obtained & relatives unwilling to give consent

Study was explained to patients in local language & written consent was taken for participation & study. IPD (indoor patient department) patients with heart failure clinically selected by using Framingham's criteria. Consecutive type of non-probability sampling was used for selection of study subjects. A total of 50 consecutive cases of heart failure with type 2 diabetes (diabetic group) and 50 consecutive cases with heart failure without diabetes (non-diabetic group) fulfilling the inclusion & exclusion criteria were included in the study after prior consent.

All patients underwent complete history taking, clinical examination, laboratory tests (CBC, Serum electrolytes, serum urea, serum creatinine), Lipid profile (serum triglyceride level, serum cholesterol level), blood sugar levels (random, overnight & fasting), HbA1c, Urine (routine & microscopy). Xray chest (PA view), Ultrasonography abdomen, ECG, 2D Echocardiography.

Parameters such as prognosis of heart failure, morbidity of patients, effect of diabetic state on heart failure, association of risk factors (hypertension, sedentary life style, Obesity/Overweight, smoking), assessment for presence of precipitating factor (Uncontrolled hypertension, arrhythmia, infection, non-compliant with diet, non-compliant with therapy, acute myocardial ischemia, anemia, dyslipidemia), causes of heart failure, (ischemic heart disease-evidences of coronary artery disease, myocardial infarction, myocardial ischemia) were studied.

Data was collected and compiled using Microsoft Excel, analysed using SPSS 23.0 version. Frequency, percentage, means and standard deviations (SD) was calculated for the continuous variables, while ratios and proportions were calculated for the categorical variables. Difference of proportions between qualitative variables were tested using chi-square test or Fisher exact test as applicable. P value less than 0.05 was considered as statistically significant.

Results

In present study, 50 patients from each group were studied. Mean age, gender of patients were comparable in both groups & difference was not significant statistically ($p > 0.05$). Ischemic heart disease dominates as a cause in two groups. Chronic pressure overload is the second most common cause in both groups, comparatively more patients of chronic pressure overload present in non–diabetic group, difference was statistically significant (p- 0.029).

Table 1: General characteristics

	Diabetic group	**Nondiabetic group**	**P value**
Mean age (mean±SD)	57.98 ± 7.636	59.68 ± 7.705	0.271
Gender			
Male	26	26	
Female	24	24	
Causes of Heart Failure			
IHD	32	24	0.1586
Chronic Pressure Overload	6	16	0.02981*
RVHD	4	3	1
Dilated Cardiomyopathy	3	3	1
Chronic Cor Pulmonale	3	4	1

In present study, 37 (74%) patients from diabetic group and 21 (42%) patients from non-diabetic group were obese/over-weight, difference was statistically significant (p-0.002).While other risk factors were comparable in both groups & difference was not significant statistically ($p > 0.05$).

Table 2: Comparison of Risk Factors

Risk factors	**Diabetic Group**	**Nondiabetic Group**	**P value**
Obesity/overweight BMI>25	37	21	0.002*
Cigarette smoking	8	10	0.794
Hypertension	16	22	0.303
Sedentary life	31	28	0.684

16 patients (32%) in diabetic group and 6 patients (12%) in non-diabetic group presented with arrhythmia, difference was statistically significant (p- 0.029). 15 patients (30%) in diabetic group and 6 patients (12%) in non-diabetic group presented with features of acute myocardial ischemia, difference was statistically significant (p- 0.049). While other factors associated with acute decompensation of heart failure such as uncontrolled hypertension, evidences of infection, history of non-compliance to advised diet, history of non-compliance to & anemia were comparable in both groups & , difference was not significant statistically ($p > 0.05$).

Table 3: Comparison of factors associated with acute decompensation of heart failure

Acute Decompensating	**Diabetic Group**	**Nondiabetic Group**	**Chi Square Df=1/ Fisher Exact Test**	**P value**
Uncontrolled HTN	8	14	1.457	0.227
Arrhythmia	16	6	4.72	0.029*
Infection	19	14	0.724	0.395
Non Compliant With Diet	20	22	0.041	0.839
Non Compliant With Therapy	12	11	0.0	1.0
Acute Myocardial Ischemia	15	6	3.858	0.049*
Anemia	23	19	0.369	0.543

On 2D Echo, affected systolic function such as ejection fraction (<20 %, 20-35 % & 35-45 %) were comparable in both groups & difference was not significant statistically (p > 0.05).
On 2D Echo, pure Diastolic Dysfunction, was comparable in both groups & difference was not significant statistically (p > 0.05). 21 patients (42%) in diabetic group and 9 patients (18%) in non-diabetic group presented with evidences Diastolic Dysfunction along with affected (reduced) ejection fraction, difference was statistically significant (p- 0.01). 38 patients (76%) in diabetic group and 23 patients (46%) in non-diabetic group presented with evidence of affected diastolic function on 2D Echo, difference was statistically significant (p-0.01).

Table 4: Comparison of 2D Echo Findings

2 D Echo findings	Diabetic Group	Nondiabetic Group	P value
Ef < 20 %	6	3	0.485
Ef 20- 35	13	18	0.387
Ef >35 to 45%	14	15	1.0
Total affected systolic function	33	36	0.665
Pure Diastolic Dysfunction	17	14	0.665
Diastolic Dysfunction with decreased EF	21	9	0.016*
Total affected diastolic function	38	23	0.0041*

Mean triglyceride level in diabetic group (212.20 ± 44.091) was more as compared to non-diabetic group (193 ± 44.733), difference was statistically significant (p- 0.033). Mean cholesterol level in diabetic group (211.80 ± 44.935) was more as compared to non-diabetic group (189 ± 42.197), difference was statistically significant (p- 0.01).
Mean serum potassium level & mean serum sodium level were comparable in both groups & difference was not significant statistically (p > 0.05). Mean serum urea level in diabetic group (55.9 ± 37.724 mg/dl) more than from non-diabetic group (35.14 ± 19.499 mg/dl), difference was statistically significant (p-0.001). Mean serum creatinine level in diabetic group (1.74 ± 1.562 mg/dl) more than from non-diabetic group (1.1 ±1.298 mg/dl), difference was statistically significant (p-0.028).

Table 5: Laboratory tests

Laboratory tests	Diabetic group	Nondiabetic group	P value
Triglyceride Level (mg/dl)	212.20 ± 44.091	193.00 ± 44.733	0.033
Cholesterol Level (mg/dl)	211.80 ± 44.935	189.00 ± 42.197	0.010
Serum Potassium level {mEq/l}	4.50 ± 0.491	4.48 ± 0.515	0.968
Serum sodium level {mEq/l}	136.36 ± 6.04	136.14 ± 5.15	0.845
Serum Urea Level (mg/dl)	55.9 ± 37.724	35.14 ± 19.499	0.001
Serum Creatinine Levels (mg/dl)	1.74 ± 1.562	1.10 ± 1.298	0.028

Mean length of hospital stay in diabetic group (6.42 ± 1.939 days) more than from non-diabetic group (4.96 ± 1.261 days), difference was statistically significant (p-0.001).

Table 6: Hospital Stay

	Diabetic Group	Nondiabetic Group	P value
Hospital Stay (days)	6.42 ± 1.939	4.96 ± 1.261	<0.001

Patients with HbA1c <8.5 has mean length of hospital stay of 5.16 ± 1.068 days. Patients

with HbA1c 8.5-9.9 have mean length of hospital stay of 7.13 ± 2.029 days. Patients with HbA1c ≥ 10 have mean length of hospital stay of 7.27 ± 1.944 days. On applying ANOVA, p value came as 0.001, showing significantly higher length of hospital stay in higher HbA1c subgroups.

Table 7: Hospital Stays according to HbA1c In Diabetic Group:

HbA1c	Hospital Stay in Diabetic Group (Mean ± SD) (days)	P value
<8.5	5.16 ± 1.068	0.001
8.5–9.9	7.13 ± 2.029	
10+	7.27 ± 1.944	

In present study, 8 patients (16%) in diabetic group and 3 patients (6%) in non-diabetic group died & difference was not significant statistically (p > 0.05).

Table 8: Mortality

	Diabetic Group	Nondiabetic Group	P value
Death	8	3	0.201

Discussion

Diabetes is a potent risk factor for HF, and the prevalence of diabetes is similar in patients with HF and reduced or preserved EF, suggesting that diabetes contributes to the pathophysiology of both forms of HF. Although diabetes predisposes to coronary artery disease, renal dysfunction, and hypertension, numerous direct effects of diabetes and hyperglycaemia on myocardial structure and function have been described.[2]

The morphological changes in the diabetic heart include myocyte hypertrophy, increased extracellular matrix (fibrosis) and intramyocardial microangiopathy. Functional changes, which may represent a continuum, include endothelial-dependent and endothelial-independent microvascular dysfunction, impaired relaxation, and increased passive diastolic stiffness and contractile dysfunction.[4,5]

Mechanisms contributing to structural and functional coronary vascular and myocardial changes are diverse and include metabolic disturbances, activation of proinflammatory and profibrotic mediators, cardiac autonomic neuropathy and increases in advanced glycation end-products (age), which promote increased collagen accumulation and increased collagen stiffness. Age accumulation may also play a role in age-related cardiovascular stiffening.[9.10]

In a study by Martens FM et al.,[11] the role of PPARs has been studied. It found that the cardiovascular risk factors like dyslipidemia, hypertension and obesity/overweight are part of the insulin resistance syndrome and are regulated by nuclear peroxisome proliferator-activated receptors(PPARs). This may be the reason for higher levels of triglycerides and cholesterol in patients from the diabetic group. Similar findings were noted in present study.

In a study by Jeffrey R. Erickson, et al.,[12] the state of hyperglycemia in type 2 diabetes acts as predisposition for development of arrhythmia. Thus, prevalence of arrhythmia was significantly higher in the diabetic group as compared to the non diabetic group with heart failure in our study, which was a finding similar to the above study.

In a study done by Danaei G et al.,[13] it was seen that diabetes was the most prevalent risk factor for cardiovascular events. Patient with diabetes mellitus have increased risk for cardiovascular disease. Acute phase hyperglycaemia and diabetes are both associated with adverse outcomes in acute myocardial infarction, with higher reported incidences of congestive heart failure, cardiogenic shock and death.

In a study by Thom N. Haase et al.,[14] it was seen that, insulin resistance, changes in

endothelial function, dyslipidaemia, diabetes were powerful risk factor for development of postinfarction heart failure. Our study showed acute myocardial ischemia prevalence was significantly higher in the diabetic group as compared to the non diabetic group with heart failure; outlining the fact that acute myocardial ischemia is a precipitating event for heart failure.

In a study by Maisch, B et al.,[15] there is an existence of diabetic cardiomyopathy in patients of diabetic heart failure. Patients in diabetic group from our study had 2D Echo features like that mentioned in different stages of diabetic cardiomyopathy. In a study by Boyer J. K. et al.,[16] there was prevalence of ventricular Diastolic Dysfunction in patients with diabetes mellitus. Diabetic patients from our study group also showed similar findings with significantly higher number of patients with diastolic dysfunction.

Our study showed diabetic state was responsible for higher length of hospital stay. In the SOLVED trial, Diabetes mellitus was a predictor of morbidity and mortality.[4] In a study by Dries D.L. et al.,[17] it was seen that there was a prognostic impact of diabetes mellitus in patients with heart failure.

In a study by TavazziL, Maggioni AP, et al,.[18] mean serum potassium level in heart failure patients was 4.3 to 4.6 mEq/l. Thus, our study results about serum potassium level are similar to the above study. Alterations of serum electrolytes in AHF are similar to those found in chronic heart failure. Hyponatremia is a common finding in AHF populations, with approximately 25 to 30 percent of patients with serum sodium level <135 mEq/l.[19] In a study (ADHERE®)[20]. Serum sodium level from heart failure population were similar to mean serum sodium level from our study.

Comorbidities like chronic renal insufficiency usually complicate patients from diabetic group making them more susceptible for deranged renal function producing higher serum urea and creatinine level. In a study done by Havranek Ep, et al.,[21] state of heart failure itself results in slight derangement of serum urea and creatinine level, added to this in diabetic group of patients comorbidities like chronic renal insufficiency add its effect to increase the serum urea and creatinine level more than that in non-diabetic patients.

Blood urea level (BUL) is more directly related to the severity of AHF than creatinine, and is typically elevated on admission. Serum BUL concentrations increase in AHF because of the decreased glomerular filtration rate (GFR) and the increased serum sodium reabsorption. Serum BUL is roughly proportional to the increased vasoconstriction in response to hemodynamic perturbations and to the neurohormonal activation in acute heart failure, with mean values of serum urea level range from 30 to 81mg/dl.[21]

In a study done by Gheorghiade M et al.,[22] mean values of serum urea level range from 30mg/dl to81mg/dl, in heart failure population. These elevations are usually accompanied by increases in creatinine, which is a more direct reflection of the decreased GFR. In study done by Havranek Ep, et al.,[21] it was seen that the state of heart failure itself results in slight derangement of serum urea and creatinine level. Besides this, in diabetic group of patients comorbidities like chronic renal insufficiency add its effect to increase the serum urea and creatinine level more than that in non-diabetic patients.

The heart failure patients in diabetic group had higher length of hospital stay than that in non-diabetic heart failure patients. There is a correlation of higher HbA1c and increased length of hospital stay in diabetic patients with heart failure.

In a study by Gebreegziabher, Y. et al.,[23] it was seen that there was a relation between admission hyperglycemia and lengthof hospital stay in patients with diabetes and heart failure. Presence of diabetes and hyperglycemia with poor glycemic control in patients with acute heart failure were associated with prolonged hospital stay. Thus the findings from our study were similar to the above studies.

In a study by Y. Y. Allen et al.,[24], there was a role of diabetic state in mortality of patients of heart failure, confirming diabetic state as a predictor of mortality in acute heart failure. Our study showed no significant difference in mortality in the two groups

Conclusion

Diabetic heart failure patients have a significantly higher likelihood to present with existence of diastolic dysfunction and also to have co-existence of both systolic as well as diastolic dysfunction. Significantly higher numbers of diabetic heart failure patients were obese/overweight, had dyslipidemia andhad deranged renal functions. They had a significantly higher chance of presenting with rales, arrhythmias and acute coronary ischaemia. Diabetic heart failure patients had a significantly longer duration of hospital stay and also had a higher chance of death during stay.

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