Frequency of Diabetes and Prediabetes in Heart Failure Patients and Their Association with In-Hospital Outcome

Noortaj Begum1*
Abu Sadique Abdullah2
Md. Aminul Haque Khan1
AN Wahida Suatana3
DMMF Osmany2
Forhadul Hoque Mollah4

1Department of Biochemistry
Enam Medical College
Dhaka, Bangladesh.
2Department of Cardiology
Bangabandhu Sheikh Mujib Medical University
Dhaka, Bangladesh.
3Dhaka Mohanagar General Hospital
Dhaka, Bangladesh
4Department of Biochemistry
Bangabandhu Sheikh Mujib Medical University
Dhaka, Bangladesh.

*Correspondence to:
Dr. Noortaj Begum
Department of Biochemistry
Enam Medical College
Savar
Dhaka, Bangladesh.
Mobile: +8801199198926
E-mail: russeldmc@yahoo.com

Abstract
Background: There are an increasing number of hospital admissions due to heart failure with diabetes or prediabetes in different hospitals in Bangladesh. But very little is known about the frequency of diabetes and prediabetes and the effect of its presence on the characteristics and outcome in patients hospitalized for heart failure. The objective of this study was to find out the frequency of diabetes and prediabetes in heart failure patients and to assess their association with in-hospital outcome.

Methods: This cross sectional analytical study was done in the department of Biochemistry and Cardiology of Bangabandhu Sheikh Mujib Medical University in collaboration with department of Cardiology of National Institute of Cardiovascular Diseases, and Dhaka Medical College Hospital from July 2010 to June 2011. After proper ethical consideration a total two hundred and fifty heart failure patients were enrolled in the study by nonrandom sampling. Fasting blood sugar was done in all patients and oral glucose tolerance test was done in patients with impaired fasting glycaemia.

Results: The frequency of prediabetes among the total population was 12.8% (95% CI, 8.7-16.8) and that of diabetes was 37.2% (95% CI, 31.2-43.2%). Improvement was achieved in 27 (84.4%) cases in prediabetic group, 75 (80.6%) cases in diabetic group and 105 (84.0%) cases in nondiabetic group. Mortality rates in prediabetes, diabetes and nondiabetes were 5 (15.6%); 18 (19.4%) and 20 (16.0%) respectively. The differences found among the three groups were not statistically significant (p>0.05). Length of hospital stay was also similar in all groups of study subjects.

Conclusion: Frequency of diabetes among heart failure patients is high and prediabetes is not negligible in our country. Future studies in this field should focus on all types of glucose abnormalities rather than previously diagnosed diabetes only.

Key words: Diabetes; heart failure; prediabetes; impaired glucose tolerance; impaired fasting glucose.

INTRODUCTION
Heart failure (HF) is a common, costly, disabling and deadly condition.1 In developing countries around 2% of adults suffer from heart failure, but over the age of 65, this increases to 6-10%2,3.

Diabetes mellitus (DM) is a common co-morbid condition of HF. It has been suggested that DM may play an important role in pathogenesis, prognosis, and response to treatment in heart failure4.

Prediabetes is referred to as borderline diabetes, impaired glucose tolerance (IGT), and/or impaired fasting glucose (IFG). Impaired fasting glycaemia or impaired fasting glucose (IFG) refers to a condition in which the fasting blood glucose is elevated above what is considered normal levels but is not high enough to be classified as diabetes mellitus. It is considered a pre-diabetic state, associated with insulin resistance and increased risk of cardiovascular pathology, although of lesser risk than impaired glucose tolerance (IGT). IFG sometimes progresses to type 2 diabetes mellitus. There is a 50% risk of progressing to overt diabetes over 10 years.

A recent study cited the average time for progression as less than three years5. IFG is also a risk factor for mortality6.
According to Tenenbaum et al in patients with ischemic heart disease, the incidence of HF at 6 to 9 years follow-up was 35.7% in nondiabetic patients, 39% in patients with impaired fasting glucose and 45.7% in diabetic patients.

Although diabetes is associated with increased incidence of heart failure, it is unclear whether increasing glucose in the absence of diabetes is a risk factor for heart failure. Subclinical states of increased blood glucose characterized as impaired glucose tolerance or impaired fasting glucose have been recognized to have pathological consequences including macrovascular diseases, increased mortality and left ventricular hypertrophy.

Now-a-days the frequency of diabetes and prediabetes in heart failure patients is increasing worldwide. Increasing trend is also seen in our country. So the aim of this study was to find out the frequency of diabetes and prediabetes in heart failure patients and to assess the associations between diabetes, pre-diabetes and in-hospital outcome of these patients.

MATERIALS & METHODS

This cross sectional analytical study was carried out in the departments of Biochemistry and Cardiology of Bangabandhu Sheikh Mujib Medical University (BSMMU), in co-operation with the departments of Cardiology, National Institute of Cardiovascular Diseases (NICVD) and Dhaka Medical College Hospital (DMCH) during the period of July 2010 to June 2011. A total of 250 hospitalized heart failure subjects, age ranging from 25-85 years, of both sexes, were selected in a nonrandom sampling technique. Cases were defined in accordance with World Health Organization criteria for diabetes or prediabetes (impaired glucose tolerance or impaired fasting glucose) and ACC/AHA ( American College of Cardiology/American Heart Association) guidelines for heart failure.

History and clinical data of all patients were collected. Fasting blood sugar was estimated after hospital admission in all subjects not known to be diabetic. OGTT was done for patients with impaired fasting glycaemia.

The patients of heart failure with asthma, chronic obstructive pulmonary disease (COPD), renal failure, liver failure, malignancy, severe anemia, pregnancy or acute myocardial infarction (MI) were excluded from the study.

Study subjects were categorized into diabetic, prediabetic and nondiabetic groups according to their blood glucose findings. Several other risk factors like hypertension, old myocardial infarction, ischemic heart disease, valvular heart disease, cardiomyopathy, and heart block were evaluated.

Frequency of diabetes and prediabetes were measured at 95% CI. In-hospital outcome was seen in respect of mortality, improvement and length of stay. Outcomes in different groups of heart failure subjects were compared by Chi-square test, unpaired t test and ANOVA test. All comparison tests were done by using computer based SPSS 16.0 for windows software. P value <0.05 was accepted as level of significance.

RESULTS

Out of the total population (n=250), 32 had prediabetes, 93 had diabetes. The frequency of prediabetes among the total population was 12.8% (95% CI, 8.7-16.8) and that of diabetes was 37.2% (95% CI, 31.2-43.2%) (Table 1). Frequency of prediabetes in total population in case of male was 10% and in case of female was 2.8%. Frequency of diabetes in male and female subjects was 29.2% and 8.0 % respectively.

### Table 1: Frequency of prediabetes and diabetes among study subjects (N=250)

<table>
<thead>
<tr>
<th>Group</th>
<th>Frequency</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Point estimate</td>
<td>95% CI</td>
</tr>
<tr>
<td>Both sex</td>
<td>32</td>
<td>12.8</td>
</tr>
<tr>
<td>Prediabetes</td>
<td>Male</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>7</td>
</tr>
<tr>
<td>Both sex</td>
<td>93</td>
<td>37.2</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Male</td>
<td>73</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>20</td>
</tr>
</tbody>
</table>

Among the prediabetic subjects frequency of IGT in total population was 7.2% (95%CI, 4.0-10.4) and that of IFG was 5.6% (95% CI, 2.7-8.5). Frequency of male and female subjects was 6.0% vs 1.2% in IGT subjects whereas 4.0% vs 1.6% in IFG subjects respectively (Table 2).

### Table 2: Frequency of IGT and IFG among study subjects (N=250)

<table>
<thead>
<tr>
<th>Group</th>
<th>Frequency</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Point estimate</td>
<td>95% CI</td>
</tr>
<tr>
<td>Both sex</td>
<td>18</td>
<td>7.2</td>
</tr>
<tr>
<td>IGT</td>
<td>Male</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>03</td>
</tr>
<tr>
<td>IFG</td>
<td>Male</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>04</td>
</tr>
</tbody>
</table>

IGT=Impaired Glucose Tolerance, IFG=Impaired Fasting Glucose

Improvement of heart failure was achieved in 27 (84.4%) cases in prediabetic group, 75 (80.6%) cases in diabetic group and 105 (84.0%) cases in nondiabetic group. Mortality rates in prediabetes, diabetes and nondiabetics were 5 (15.6%); 18 (19.4%) and 20 (16.0%) respectively. The differences found among the three groups were not statistically significant (p>0.05) (Table 3). Length of hospital stay was also similar among all groups of study subjects (6.6±0.9 days in prediabetic subjects, 6.9±1.9 days in diabetic subjects & 6.7±2.1 days in nondiabetic subjects, P>0.05) (Table 4).
In the Danish Investigation of Arrhythmia and Mortality On Dofetilide (DIAMOND) Heart Failure Trial, which included consecutive admissions to 34 Danish hospitals between November 1993 and December 1995 with new or worsening HF, 16% of patients were diabetic. Diagnosis of diabetes was based on a self-report by the patient or by documentation in the patient’s medical records. Possible explanations of higher prevalence of diabetes in North American subjects are differences in the etiology of HF in those populations. For example, diabetes may be more common in patients with ischemic heart disease than in those with HF due to other causes. Differences in definitions or methods of diagnosis may also explain geographic variation.

Another important outcome of our study was the frequency of prediabetes in patients with HF. The frequency was 12.8% in total population, among them IGT was 7.2% and IFG was 5.6%

The prevalence of prediabetes among patients with HF is less well documented, and there is even less information on incidence of IGT. The prevalence of glucose intolerance in patients with HF was reported in several trials range from 23% to 43%24,25. A recent study conducted in Kameda Medical Center, Chiba, Japan showed that out of 136 subjects 46 (33.82%) had prediabetes, among them 9 (9.6%) had IFG, 37 (39.4%) had IGT 26.

This wide range reflects the diverse criteria and methods used to identify patients with glucose intolerance. Many studies investigating the prevalence of dysglycemia in HF used fasting or casual glucose levels or only HbA1c. Fasting plasma glucose and HbA1c have limited sensitivity for diagnosis of glucose intolerance, in particular IGT. For example, Egstrup et al reported that omitting OGTT would have misclassified 40% of newly diagnosed cases of diabetes, and by definition all patients with IGT among patients with HF 27.

The prevalence of diabetes among patients with HF depends on various factors. One possible explanation is the presence of other metabolic disorders such as obesity, hyperlipidemia, and hypertension. These factors may increase the risk of developing diabetes and contribute to the increased prevalence of diabetes in patients with HF.

It is important to note that the prevalence of diabetes and prediabetes in patients with HF may vary depending on the definition used and the methods of diagnosis. Therefore, it is important to standardize the definition and methods of diagnosis across studies to allow for better comparison and interpretation of results.

In conclusion, the prevalence of diabetes and prediabetes in patients with HF is high and varies depending on the definition used and the methods of diagnosis. Further research is needed to better understand the factors that influence the prevalence of diabetes and prediabetes in patients with HF and to develop effective interventions to prevent and manage these conditions.

### Table 3: Outcomes of study subjects (N=250)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Group I (n=32)</th>
<th>Group II (n=93)</th>
<th>Group III (n=125)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>Expired</td>
<td>5</td>
<td>15.6</td>
<td>18</td>
<td>19.4</td>
</tr>
<tr>
<td>Improved</td>
<td>27</td>
<td>84.4</td>
<td>75</td>
<td>80.6</td>
</tr>
</tbody>
</table>

P value was reached from chi square test.

### Table 4: Distribution of the study subjects according to duration of hospital stay (N=250)

<table>
<thead>
<tr>
<th>Duration (day)</th>
<th>Group I (n=32)</th>
<th>Group II (n=93)</th>
<th>Group III (n=125)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>1 – 5</td>
<td>10</td>
<td>31.25</td>
<td>30</td>
<td>32.6</td>
</tr>
<tr>
<td>6 – 10</td>
<td>20</td>
<td>62.5</td>
<td>49</td>
<td>52.69</td>
</tr>
<tr>
<td>&gt;10</td>
<td>02</td>
<td>6.25</td>
<td>14</td>
<td>15.05</td>
</tr>
<tr>
<td>Mean±SD</td>
<td>6.6±0.9</td>
<td>6.9±1.9</td>
<td>6.7±2.1</td>
<td>0.112</td>
</tr>
<tr>
<td>Range (min-max)</td>
<td>(4-11)</td>
<td>(2-14)</td>
<td>(2-14)</td>
<td></td>
</tr>
</tbody>
</table>

P value was reached from ANOVA test.

## DISCUSSION

The prevalence of HF with diabetes has accelerated dramatically over the past decades, with 16.9% in the late 1990s rising up to 29.1% in recent years. Our study also reveals very high frequency of DM (37.2%) among hospitalized patients with HF.

Prevalence similar to the current study has also been observed in different studies. In European cohort studies of unselected, unplanned HF admissions, the prevalence of diabetes was found 21% in a French cohort 21. The prevalence of HF with diabetes has accelerated dramatically over the past decades, with 16.9% in the late 1990s rising up to 29.1% in recent years. A recent study conducted in Kameda Medical Center, Chiba, Japan showed that out of 136 subjects 46 (33.82%) had prediabetes, among them 9 (9.6%) had IFG, 37 (39.4%) had IGT 26.

Possible explanations of higher prevalence of diabetes in North American subjects are differences in the etiology of HF. For example, diabetes may be more common in patients with ischemic heart disease than in those with HF due to other causes. Differences in definitions or methods of diagnosis may also explain geographic variation.

Another most important outcome of our study was the frequency of prediabetes in patients with HF. The frequency was 12.8% in total population, among them IGT was 7.2% and IFG was 5.6%.

This wide range reflects the diverse criteria and methods used to identify patients with glucose intolerance. Many studies investigating the prevalence of dysglycemia in HF used fasting or casual glucose levels or only HbA1c. Fasting plasma glucose and HbA1c have limited sensitivity for diagnosis of glucose intolerance, in particular IGT. For example, Egstrup et al reported that omitting OGTT would have misclassified 40% of newly diagnosed cases of diabetes, and by definition all patients with IGT among patients with HF.

In our study, diabetes was associated with 19.4% in-hospital mortality whereas mortality rate was 15.6% in prediabetic group and 16% in nondiabetic group. These differences of mortality were not statistically significant.

The finding of this study is consistent with a number of studies abroad 14,15,16,17. In Randomized Evaluation of Strategies for Left Ventricular Dysfunction (RESOLVD), diabetic patients had an increased mortality rate, whereas nondiabetic patients also had a similar prognosis. Analysis of short-term clinical outcomes in the OPTIMIZE-HF registry demonstrates that in-hospital mortality rates were similar in patients with DM and those without.

The TEMISTOCLE (heart failure epidemiological study in Italian people) study showed that in diabetic patients with heart failure all-cause in-hospital mortality rate was similar between diabetics and non-diabetics (5.3 vs 5.7%, p>0.05) 29.

The report of some studies did not support our result. The presence of DM in patients with HF has been associated with an increased risk of poor outcomes 22,23,24,25. An analysis from the Studies of Left Ventricular Dysfunction trials and registry program demonstrated that the presence of DM in patients with HF resulted in an increased risk for mortality 30.
The Beta-Blocker Evaluation of Survival Trial reported a DM prevalence of 36% among patients with HF enrolled, and on multivariable analysis showed that DM was independently associated with a 22% increased risk of all-cause mortality.

One of the aims of our study was to see the length of hospital stay which is an important tool for in-hospital outcome. Mean duration of hospital stay in heart failure subjects with diabetes was 6.9 days, prediabetes was 6.6 days and with nondiabetes was 6.7 days. But these differences were not statistically significant.

This finding is not consistent with that of some other studies. Kapoor et al showed that diabetes was independently associated with longer hospital stay but not in-hospital mortality. OPTIMIZE-HF registry demonstrates that patients of HF with DM had longer length of hospital stay and higher re-hospitalization rates compared with HF patients without DM.

In the Reykjavik study, IGT was shown to be an independent predictor of all-cause mortality to a similar degree to that of DM. In a recent study carried out in Division of Cardiology, Department of Medicine, Kameda Medical Center, Chiba, Japan, it was shown that HF patients with IGT tended to have a higher mortality rate than those without glucose intolerance. Two meta-analyses showed that only post-prandial hyperglycemia, but not fasting hyperglycemia, is a good predictor of adverse cardiovascular events.

In our study outcome scenario was identical in IGT and IFG and DM subjects which was not consistent with previous results. This was possibly from the fact that we only included the hospitalized heart failure subjects and in-hospital outcome was based on mortality and length of hospital stay whereas, in other studies they included both inpatient and outpatient department and long term cohort study was done there. The diagnosis of IGT & IFG in the Reykjavik study, however, was done on 50 gm OGTT, not 75 gm was used in the present study. The European Guidelines on diabetes, prediabetes, and cardiovascular diseases recommend use of 75-g OGTT.

In this study, we had several limitations. This study was based on a small number of patients. This present study included only patients with HF who required hospitalization, and thus the data described here cannot be extrapolated to the whole HF population. Information regarding the degree of glycaemic control and diabetes medications other than insulin was not taken properly. For outcome measurement we only evaluated mortality and duration of hospital stay.

CONCLUSION
Prediabetic patients are prone to develop diabetes later in life. With appropriate measures to control prediabetes, the development of frank diabetes and worse outcome in heart failure patients may be prevented. Further large-scale, prospective clinical trials are necessary to evaluate long term mortality and morbidity of patients of heart failure with diabetes or prediabetes.

DISCLOSURE
All the authors declared no competing interest.
REFERENCES