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Original Research Article

New Onset Diabetes in Patients of Dilated Cardiomyopathy

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Conflict of interest: Nil

Abstract:

Background: Diabetes mellitus (DM) significantly increases the likelihood of developing new-onset heart failure (HF). The intricate pathogenesis of HF in individuals with DM is primarily linked to the detrimental cardiovascular impacts of elevated blood sugar levels and associated metabolic irregularities, often referred to as diabetic cardiomyopathy. The emergence of new-onset type 2 diabetes mellitus in the context of heart failure, termed cardiogenic diabetes mellitus is insufficiently examined and documented in the medical literature.

Methods: The study was conducted on 100 patients with newly diagnosed cases of idiopathic dilated cardiomyopathy from the period 1st April 2017 to 31st March 2020 who were on monthly follow-ups since then. All patients included in the study were non-diabetic at the time of enrollment and for a minimum period of six months thereafter. The establishment of diagnosis of diabetes in the study population was according to the standards of medical care in diabetes- American Diabetes Association guidelines – 2014.

Results: 45 patients were male with a mean LVIDD (left ventricular internal diameter in diastole) diameter of 6.2 mm ± 1.3 (95% CI, 5.4-7.2), LVEF (left ventricular ejection fraction) of 28% (95% CI,18-45%). Out of the 100 patients 33 patients developed type 2 diabetes over a period of one year.

Conclusions: This study showing a high incidence of new onset diabetes in patients of heart failure with reduced ejection fraction (HFrEF). The cause may be drug induced by beta blockers or diuretics used for a prolonged period, a genetic predisposition having a common gene for the two diseases, a common pathophysiological pathway or may be due to emotional and environmental factors.

Keywords: Diabetes Mellitus, Dilated Cardiomyopathy, New Onset, Incidence.

Introduction

Diabetes mellitus (DM) emerges as a substantial risk factor for numerous cardiovascular (CV) outcomes, notably heart failure (HF) [1,2]. The worldwide prevalence of diabetes is anticipated to rise from 8.8% in 2015 to 10.4% by 2040. India ranks second, with 69.2 million adults (9%) affected by diabetes, and projections indicate that by 2040, this number is expected to escalate to 123.5 million [3]. Epidemiological and observational investigations consistently reveal that DM independently amplifies the risk of new-onset HF, regardless of other conventional risk factors. A 1% increase in glycated haemoglobin A1c corresponds to a 30% increase in HF risk in Type 1 DM (T1DM) [4] and an 8% increase in HF risk in Type 2 DM (T2DM), the predominant form affecting approximately 90% of individuals with diabetes [5]. Studies indicate that the prevalence of cardiac dysfunction in those with T1DM and T2DM can reach as high as 14.5% and 35.0%, respectively [6,7]. The Framingham Heart Study, which followed 5209 men and women for 18 years, disclosed that women with diabetes mellitus (DM) experienced a fivefold higher incidence of heart failure (HF) in comparison to men, who showed a 2.4-fold increase. These results held steady even after accounting for additional risk factors like age, coronary artery disease (CAD), and hypertension (HTN) [8]. Insulin resistance (IR) in Type 2 diabetes mellitus (T2DM) is a key player in cardiovascular (CV) disease development. It disrupts glucose metabolism, causing chronic hyperglycemia, oxidative stress, and inflammation, leading to cellular damage. IR also impacts

systemic lipid metabolism, contributing to dyslipidemia. When combined with endothelial dysfunction, these factors promote atherosclerotic plaques and myocardial damage through altered signal transduction, substrate metabolism disturbances, and modifications in substrate delivery.

Subsequent pathophysiological steps involve impaired mitochondrial Ca2+ handling, autonomic neuropathy, and activation of the renin–angiotensin–aldosterone system, inflammation, endoplasmic reticulum stress, cardiomyocyte death, and microvascular dysfunction. This results in a loss of metabolic flexibility, with increased reliance on glycolysis and ketone body oxidation for energy and decreased glucose oxidation in mitochondrial oxidative metabolism [9].Chronic heart failure (HF) is characterized by insulin resistance (IR), a state where the body's cells exhibit decreased responsiveness to insulin.

IR is prevalent in over half of the patients with HF. While the precise origins of insulin resistance (IR) in heart failure (HF) remain incompletely understood, several significant mechanisms have been suggested, encompassing oxidative stress, inflammation, mutations in insulin receptors, endoplasmic reticulum stress, and mitochondrial dysfunction [10].The current study aimed to find the incidence of new onset diabetes and its clinical & biochemical profile in patient of established heart failure with reduced ejection fraction (HFrEF).

Methods:

This is an observational, descriptive, case-series report of 100 patients ranging from 30-65 years who were enrolled and whose complete disease-related data was captured in the cardiology database and case records section of Shadan Institute Of Medical Sciences and data analyzed after the study period with due permission from the institutional ethics committee.

Strict inclusion & exclusion criteria were followed for the patients enrolled. The period of data collection was from 1st April 2017 to 31st April 2020 and data was analysed thereafter. All the patients were regularly attending the monthly follow-up for three years according to the study protocol.

All the patients enrolled had been diagnosed with dilated cardiomyopathy defined as LVEF ≤35% with dilated LV (male>58mm and female>55mm) established by echocardiography first time in the cardiology outpatient department of Shadan Medical & General Hospital and underwent the routine basic investigations of ECG, echocardiography, complete hemogram, blood glucose estimation (R/F/PP) every three months. Apart from this, those suspected of any further derangements were advised for any of the following investigations: Glycosylated haemoglobin, complete lipid profile, thyroid profile, renal profile and liver profile. Further for the study purpose parameters like serum uric acid, ferritin, 25-OH-VIT D, and homocysteine were measured at the establishment of DCM diagnosis and the end of the study period for those patients enrolled in the study.

At the end of the study period complete baseline characteristics and the changes of the various clinical, echo-cardiography and biochemical parameters were noted in a master chart worksheet and looked for any significant outcome for a hypothesis generation. Various past research articles linked to the proposed hypothesis from 1980 till date were thoroughly analyzed from the pub PubMed Central and Google search and an attempt was made to explain the hypothesis and present it for future case-control and cohort studies.

Inclusion Criteria

- Patients should be non-diabetic at the establishment of HFrEF.
- All patients with comparable demographic profile

Exclusion Criteria

- Patients associated with any other metabolic disorders including obesity.
- A very strong family history of diabetes mellitus
- Patient with any malignancies
- Valvular heart disease,
- End-stage chronic kidney disease (estimated glomerular filtration rate<30ml/min

Laboratory Investigations: All routine investigations were done. Investigations on demand were done by other laboratories. The samples were collected at the hospital and transported to Thyrocare collection wing in the city.

Statistical Analysis: Blood glucose and glycosylated hemoglobin (GlyHb) were log transformed to obtain normal distribution. Student's T test was used to compare the mean of continuous variable. Chi square test was used to study the relationship between GlyHb and the other parameters (independent variables). Pearson's co-relation coefficient was used to look for association among risk factors. All the groups were combined for Pearson's correlation analysis. All analysis was performed using SPSS software system package version 22 and P value < 0.05 was concluded as the level of significance. A method of complete case analysis was followed.

Results

Our study showed the incidence of new-onset diabetes mellitus to be 33%. 11 patients were lost to follow up and 8 patients had missing data. Chi-square test analysis for all independent variables did not show any relationship between GlyHb and other parameters (P> 0.05, Table 1). The predictive value of multiple regression with GlyHb and other co-variates was found to be insignificant (P>0.05, Table 2). Therefore it was concluded that the onset of diabetes mellitus was not associated with any risk factors in our study group and so we hypothesized the other probable reasons for the same.

Table 1: Pearson's Chi-square test showing an association between Glycosylated haemoglobin (GLCYHb) with other variables at P-value < 0.05 was compared for all statistical analyses and was found that an association was not found between the studied variables.

Variable	P Value
GLCYHb * serum ferritin	0.389
GLCYHb* Vitamin D	0.071
GLCYHb* Homocysteine	0.129
GLCYHb* Body mass index	0.389
GLCYHb* waist Circumference	0.103

Table 2: Multiple linear regression was applied to predict GLCYHB with the studied variables, R^2 = 0.259375 the predictive value was observed to be insignificant

	Co-Efficient	Standard Error	T Stat	P Value	Lower 95%	Upper 95%
Intercept	6.9486	2.03	3.4225	0.002	2.75	11.14
Age	-0.00025	0.01	-0.0242	0.98	-0.02	0.02
Bmi	0.046748	0.41	1.1377	0.27	-0.04	0.131
Waist Circumference	0.009884	0.0154	0.64	0.55	-0.022	0.042
TNF -alpha	-0.0036	0.003	-1.205	0.24	-0.009	0.0025
Uric Acid	-0.313	0.206	-1.52	0.142	-0.74	0.113
SF AFT	0.0009	0.0015	0.609	0.55	-0.0023	0.004
Vit D	0.015	0.033	0.442	0.6622	-0.055	0.085
HCY AFT	0.006	0.0077	0.83	0.415	-0.009	0.022
CRP	-0.796	0.821	-0.97	0.34	-2.49	0.902

Discussion

The most important finding of our study was that the incidence of new-onset diabetes in the patients of established HFrEF was relatively high about 33%. The mean age of onset of diabetes in our patients is 42 years. Patients with new-onset diabetes have relatively stable LV ejection fraction over time and in about 20% improved over time to mild LV dysfunction.

The most frequent symptom of this new-onset diabetes was increased thirst and frequency being on the same dose of diuretics and the same LV systolic function. The average mean duration onset of diabetes from diagnosis and first hospitalization of Heart failure was about 11 months. All the patients have normal coronary angiograms and need one or two medications in mild to moderate doses to become euglycemic. This may be due to overemphasis on diet restriction in heart failure as well as a low insulin resistance state unlike denovo Diabetes without heart failure.

Paradoxically, these patients had recurrent heart failure admissions before the diabetes onset but after the onset of diabetes, the frequency of hospitalization reduced. This paradoxical effect may be due to the addition of SGLT2 inhibitors at the outset of diagnosis, unlike other patients with heart failure where there is inertia in starting SGLT2 inhibitors. Metabolic impairment is intrinsic to HF pathophysiology and insulin resistance is present in up to 60% of patients with HF [11]. Among nondiabetic patients with HF enrolled in the CHARM Program (Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity) and EMPHASIS-HF (Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure), the incidence of DM was 28 and 21 per 1000 person-years, respectively, which is substantially higher than adults of similar age in the general population (9.4–10.9 per 1000 person-years for adults 45 and older) [12,13,14].

The predictors of incident DM among patients with HF include elevated body mass index and waist circumference, history of smoking, elevated glucose or HbA_{1c}, higher systolic blood pressure, longer duration of HF, diuretic therapy, and higher New York Heart Association functional class [15]. Chronic heart failure (HF) is characterized by insulin resistance (IR), a condition observed in over half of HF patients. This IR is linked to impaired cardiac innervation, as evidenced by decreased early and late heart-to-mediastinum ratios and

washout rate in 123I-MIBG imaging, indicating heightened activity of the cardiac sympathetic nervous system [16]. Furthermore, IR is connected to an overactive renin–angiotensin–aldosterone system (RAAS) attributed to compromised insulin action [17]. Many studies investigated the prevalence of dysglycemia in HF. An extensive literature survey shows some common factors in the pathophysiology of DCM and diabetes. Oxidative stress is common in both DCMP and diabetes. AGE receptor expression is induced by oxidative stress [18,19]. Increased formation of AGEs secondary to hyperglycemia may alter structural proteins & exacerbate the chronic inflammatory process. Diabetes is a pro-inflammatory disease similar to dilated cardiomyopathy with increased tissue concentration of cytokines [20]. Studies have implicated diabetes-induced or glucose-dependent modifications of ca2+/camodulin-dependent PK2 leading to glucose-derived modifications of cardiac contractile dysfunction in diabetes as well as in dilated cardiomyopathy per se [21].

Cardiac muscles are one of the high-energy demanding tissues and therefore cardiac involvement occurs in large number of mitochondrial diseases manifesting as cardiomyopathy [22]. Cardiac insulin signalling mechanism mediates cellular homeostasis via control of protein synthesis, substrate usage and cell survival. The connection between abnormal insulin signalling and heart failure arises in part from the established epidemiological association between obesity, type 2 DM, insulin resistance and heart failure. Moreover, studies in humans and animal models have revealed that heart failure is associated with generalized insulin resistance [23].

Apoptotic and necrotic cell death have been implicated in the pathology of both diabetes mellitus and cardiomyopathy [24,25].The infectious–immune theory has long been hypothesized to explain the pathogenesis of many unrecognized dilated cardiomyopathies as a result of cardiac remodeling [26]. The assumption that the pathogenesis of type -2 DM also encompasses autoimmunity is gaining importance based on the presence of circulating autoantibodies against B cells and self-reactive T cells [27].

Both DM & DCMP have genetic causative factors involving polymorphism [28]. Beta-blockers, thiazide and thiazide-like diuretics on prolonged and regular use cause development of long-standing hyperglycemia [29].In some recent studies, it was observed that hyperuricemia has a role in the development of metabolic syndrome, Coronary artery disease and DM. Higher levels of serum uric acid were associated with increasing risk of DM [30,31]There needs to be studies conducted to identify any common genetic mutations if at all one exists.

With India and other developing countries becoming a hub of diabetes and DCM, there is a need for introspection as to whether there exists any association between these two diseases as both are genetically predisposed and in 80% of cases idiopathic in origin. As there exist secondary causes to DCMP so also there exist secondary causes to the development of DM; like long-term usage of specific drugs, post-transplantation effect or association of diabetes with multifactorial syndromes. The study of this association will help to predict in future the status of diabetes in DCMP or vice-versa. Hence this study was conducted to predict certain associations and outcomes for patient education, precautions and prevention.

Conclusion

To our knowledge, this is the first report on the incidence of new-onset diabetes in patients of established heart failure with reduced ejection fraction (HFrEF). We recommend that patient with heart failure should be closely looked for symptoms of diabetes and biochemically blood parameters should be checked.

Limitations- First, this study was based on a small number of patients at a single center. The cohort in the present study included only patients with HF who required hospitalization, and thus the data described herein cannot be extrapolated to the whole HF population. We did not evaluate diastolic function on echocardiography because the subjects included a considerable number of patients with atrial fibrillation.

Finally, the presence or absence of glucose intolerance was determined by the attending physician who also decided whether admission for treatment was required, and this may have affected the rate of readmission in the present study.

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