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Are We Missing Out the Real Culprit of Diabetes Cardiomyopathy?

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Abstract

Introduction: *Many studies have been focusing on diabetes related ischemic heart disease and heart failure, but not on the main culprit which is myocardial fibrosis (MF). Fifty percent of well controlled DM patients are liable to some degree of cardiac dysfunction even after being normotensive only. The real culprit of DCM is usually missed out as well controlled diabetic patients are asymptomatic and there is delay in both the diagnosis and treatment of MF.*

Method: *An in-depth exploration and meta-analysis of various studies identifying the cause/mechanism, investigation and management of diabetes related myocardial fibrosis.*

Results: *A fibrogenic program is activated due to hyperglycemia which leads to accumulation of advanced glycation end products (AGEs) responsible for promoting fibrosis. CMRI with LGE is the gold standard in diagnosing MF. Tissue inhibitor of mettaloproteinase 1 (TIMP1) level is associated with cardiac fibrosis in T2DM patients. Systemic ET and spironolactone have a therapeutic effect in in diabetic cardiomyopathy. Stem cells could inhibit fibrosis via releasing paracrine factors which consequently produce the effect on extracellular matrix (ECM).*

Conclusion: *Stem cell treatment could be a hot topic for research for attenuating MF as it would lead to significant reduction in mortality rate of diabetes related heart failure patients.*

Introduction

According to WHO, the number of people with diabetes mellitus (DM) has risen by four folds in four decades from1980 to 2014. DM is more prevalent in developing countries than in developed countries and has been identified as the ninth leading cause of death in 2019. In India, it comprises of about 8.7% in the age group of 20 - 70 years.

Diabetic Heart Disease (DHD)

Many studies have been focusing on diabetes related ischemic heart disease and heart failure, but this is an in-depth exploration and meta-analysis of various studies including in vivo and in vitro research as well as clinical research identifying the cause/mechanism, investigation and management of diabetes related myocardial fibrosis (MF) as those patients have worse clinical outcomes.

DM and Heart failure (HF) are inter-related, with the prevalence of later of about 20%. DHD could be asymptomatic in its early stages leading to under-recognition and delay in treatment. Fifty percent of well controlled DM patients are liable to some degree of cardiac dysfunction even after being normotensive only. As the life expectancy is increased, there is an epidemic of HF. According to the Framingham Heart Study, incidence of HF is increased by 2.5-fold in diabetics irrespective of hypertension, hyperlipidemia and coronary artery disease and is doubled in females.

Diabetic cardiomyopathy (DCM) occurs due to abnormlity in cardiac structure as well as its function irrespective of its macrovascular complications. DM is associated with MF which reduce myocardial compliance, leading to diastolic dysfunction which may consequently lead to heart failure or arrhythmias despite normal left ventricular systolic function. Interstitial MF is the key feature of DHD as identified by Rubler et al.

Mechanism

When compared to non-diabetic, MF is confirmed in DM via increased deposition of interstitial collagen types I and III in myocardial biopsies.

Following factors leading to MF have been identified:

- Increased production of advanced glycation end products (AGEs),
- Renin-angiotensin-aldosterone activation
- Neurohumoral pathway

- Mitochondrial dysfunction
- Increase in oxidative stress
- Inflammation

As hyperglycemia activates a fibrogenic program, it leads to accumulation of AGEs which crosslink with extracellular matrix (ECM) proteins and promotes fibrosis.

DCM is characterized by normal LV systolic function but abnormal LV diastolic function due to delay in LV filling as well as its relaxation. Increased LV mass in DM is not solely due to LV hypertrophy but it is the combined consequence of cardiac fibrosis, hypertrophy and cell loss via apoptosis.

Investigations

Presence of cardiac fibrosis in diabetics is a sign poor prognosis. It is one of the major factor affecting major adverse cardiovascular events. As presence of DM associated cardiac fibrosis is even prior to ischemic injury, it is crucial to detect as early as possible.

Among the noninvasive approaches for detecting cardiac fibrosis like echocardiography-derived integrated backscatter and cardiac magnetic resonance imaging (CMRI), CMRI with late gadolinium enhancement (LGE) is considered the primary option.

With increased galectin 3 and tissue inhibitor of mettaloproteinase 1 (TIMP1), T2DM are also known to have increased prevalence of LGE MRI.

Management

It is known that exercise is beneficial for both diabetes and myoacardial issues but Dede et al described in detail how systemic exercise training (ET) could have a beneficial effect in DCM. His team conducted the study for 8 weeks randomizing 36 mice into 3 groups; Diabetic control, Diabetic exercise (DE) and non - diabetic control.

DE group, where diabetic mice had undergone ET program showed some improvement in their cardiac function when echo was done prior to euthanasia as well increased concentrations of ECM proteins, MMP-9 and TIMP-1 in post–mortem.

Increased cardiac biomarkers are found in DM suffering from HF with reduced ejection fraction (HFrEF). But TOPCAT's North American cohort study gathered data from 124 diabetic HF patients with preserved ejection fraction (HFpEF) versus 124 non DM for 12 months to check the level of these

biomarkers and the effect of spironolactone on them. DM was also found to be associated with increased biomarkers in HFpEF patients. Moreover, spironolactone changed hs-TnT and TIMP-1 levels showing anti-fibrotic action.

Cell therapy could be an alternative to traditional management of myocardial infarction (MI) as it can put a stop to cardiac fibrosis, the main culprit in progressing towards heart failure. However, ElNakish et al wanted to find out whether this effect was due to replacement of dead cardiomyocytes or other factors. They demonstrated that this effect was mainly due to the direct effects of paracrine factors released from stem cells on the ECM which could halt fibrosis.

Conclusion and Recommendations

A fibrogenic program activated due to hyperglycemia leads to accumulation of advanced glycation end products (AGEs) responsible for promoting fibrosis.

CMRI with LGE is the gold standard in diagnosing MF.

Tissue inhibitor of mettaloproteinase 1 (TIMP1) level is associated with cardiac fibrosis in T2DM patients.

Systemic ET and spironolactone have a therapeutic effect in in DCM.

Stem cells could inhibit fibrosis via releasing paracrine factors which consequently produce the effect on extracellular matrix (ECM).

Stem cell treatment could be a hot topic for further researches focusing on MF attenuation as it would lead to significant reduction in mortality rate of diabetes related heart failure patients.

References

1. WHO Diabetes Facts, last updated 10 Nov 2021, accessible at https://www.who.int/en/news-room/fact-sheets/detail/diabetes

2. WHO Diabetes India Facts and Figures, last updated 14 Nov 2019, accessible at https://www.who.int/india/Campaigns/and/events/world-diabetes-day

3. Ritchie R.H. et al, Basic Mechanisms of Diabetic Heart Disease, AHA Circulation Research, Vol 126, Pg 1501–1525, last updated at 21 May 2020, accessible at https://doi.org/10.1161/CIRCRESAHA.120.315913

4. Connelly K. A. et al, Diabetes and Myocardial Fibrosis: Is CMR the Force Leading to the Rise of "Scar Wars"?, JACC Journal, Vol 15, No. 5, Pg 5809 – 5811, last updated at 15 May 2022, accessible at https://www.jacc.org/doi/10.1016/j.jcmg.2022.01.015

5. Luneva E.B. et al, Simple Predictors for Cardiac Fibrosis in Patients with Type 2 Diabetes Mellitus: The Role of Circulating Biomarkers and Pulse Wave Velocity, Journal of Clinical Medicine, Vol 11, Issue 10, Pg 2843,last updated at 18 May 2022, accessible at https://doi.org/10.3390/jcm11102843

6. ElNakish M.T. et al, Stem cell transplantation as therapy for cardiac fibrosis, Journal of Pathology 2013, Vol 229, Issue 2, Pg 347 – 354, accessible at DOI: 10.1002/path.4111, last available at 28/2/2022

7. Dede E. et al, The effects of exercise training on cardiac matrix metalloproteinases activity and cardiac function in mice with diabetic cardiomyopathy, Biochemical and Biophysical Research Communications Volume 586, Pg 8-13, Last updated at 1 January 2022, accessible at https://doi.org/10.1016/j.bbrc.2021.11.013

8. ElNakish M. T. et al, Stem cell transplantation as a therapy for cardiac fibrosis, The Journal of Pathology, Vol 229, Issue 2, Pg 347 to 354, last updated at Jan 2013, accessible at https://doi.org/10.1002/path.4111