



Early Detection and Prevention of Diabetic Cardiomyopathy in Pediatric Age Group

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Type 1 diabetes mellitus (DM) is one of the most common chronic diseases in children with long-term serious complications including cardiac impairment that constitutes one of the most common causes of death in these children. Diabetes is a major risk factor for cardiovascular disease (CVD) including the cardiac muscle, causing both systolic and diastolic cardiac dysfunction. The etiology of the diabetes-associated cardiovascular morbidity and mortality is not completely clear [1].

The development of Diabetic cardiomyopathy (DCM) is multifactorial and several pathophysiologic mechanisms have been proposed to explain structural and functional changes associated with DCM [2]. Oxidative stress plays a critical role in DCM development, it has numerous deleterious effects on cardiovascular system through direct cellular damage of proteins and DNA and activation of apoptosis and redox transcription nuclear factor- κ B (NF- κ B) which stimulates the production of inflammatory mediators (such as tumor necrosis factor- α (TNF- α), interleukin-1 β (IL-1 β)) [3]. These inflammatory mediators can modulate cardiac function, stimulate apoptosis and contribute to development of DCM [4].

Increased cardiac cell death also plays an important role in the development of DCM. Both apoptosis and necrosis were observed in the hearts of type 1 and 2 diabetes [5]. Hyperglycemia, oxidative stress and inflammation are the main causes of induction of cardiac cell apoptosis in diabetic heart [6].

The primary structural changes observed in DCM are cardiac fibrosis and accumulation of extracellular matrix proteins, particularly collagen. Collagen accumulation in diabetic myocardium may be due either excessive production of collagen by fibroblasts or from decreased degradation of collagen by matrix metalloproteinases (MMPs). Hyperglycemia and oxidative stress cause abnormal gene expression that alter signal transduction, notably activation

of NF- κ B, which up-regulates several genes correlated to fibrosis, including transforming growth factor- β (TGF- β), in diabetic heart [2,7].

In a previous study, we proved that diabetic patients had significant lower level of glutathione and significant higher levels of malondialdehyde (MDA), nitric oxide, tumor necrosis factor- α (TNF- α), Fas Ligand (Fas-L), matrix metalloproteinase-2 (MMP-2) and troponin-I than control subjects. Increased expression of transforming growth factor- β (TGF- β) mRNA in peripheral blood mononuclear cells was also observed in diabetic patients. 2D global longitudinal strain and 3D longitudinal, circumferential and area strain were significantly decreased in diabetic children. α -lipoic acid significantly increased glutathione level and significantly decreased MDA, nitric oxide, TNF- α , Fas L, MMP-2, troponin I levels and TGF- β gene expression levels. Moreover, α -lipoic acid significantly increased mitral e/a ratio, ventricular global peak systolic strain in diabetic patients. There was significant negative correlation between Global peak systolic strain (G) and glutathione and significant positive correlations between G and glutathione ($r = 0.515$) and significant negative correlations between e/a and MDA, NO, TNF- α and Fas-L were also observed. MDA, NO, TNF- α and Fas-L. In addition, a significant positive correlation between e/a ratio and glutathione ($r = 0.515$) and significant negative correlations between e/a and MDA, NO, TNF- α , and Fas-L were also observed. These data suggest that oxidative stress, inflammatory cytokines such as TNF- α , apoptosis and fibrosis play a role in the development of diabetic cardiac dysfunction and that α -lipoic acid may have a beneficial role in the management of type 1 diabetic patients as a cardioprotective therapy and prevention of development of diabetic cardiomyopathy. This cardioprotective effect can be explained by the antioxidant, anti-inflammatory, anti-apoptotic and anti-fibrotic properties that ALA showed in type 1 diabetic patient [8].

In another research, we evaluated RV function in 30 children with type-1 diabetes mellitus compared to 30 matched healthy children as a control group. We evaluated RV functions using conventional echocardiography beside using new echocardiographic modalities such as speckle tracking imaging, tissue Doppler imaging, and real-time three-dimensional echocardiography (RT3DE). Moreover, we measured serum resistin level in these children using enzyme-linked immunosorbent assay (ELIZA). The two groups were comparable regarding left ventricular systolic and diastolic functions when measured by conventional echocardiography. However, both LV systolic and diastolic functions were found to be impaired using recent echocardiographic modalities in the form of significant decrease of LV myocardial performance index (MPI), mitral annulus E'/A' wave, and 3D-LV EF in diabetic children compared to healthy controls. Similarly, RV function was significantly impaired in diabetic children compared to healthy controls as detected by recent echocardiographic modalities in the form of significant difference in annular systolic excursion (TASE), right ventricular longitudinal systolic strain (RV LSS), MPI, pulmonary artery pressure, and 3D-RV EF. Yet, conventional echocardiography failed to reveal any RV function impairment. Age was significantly positively correlated with serum resistin level in such children. While, both TASE and RV LSS were significantly negatively correlated with serum resistin levels. From this study, we revealed the subclinical impairment of RV systolic and diastolic dysfunction in children with type-1 diabetes mellitus that was positively correlated with serum resistin level in such children [9].

In more recent study, we evaluated the role of three-dimensional speckle tracking echocardiography (3D-STE) in the detection of subclinical myocardial dysfunction in asymptomatic children with type 1 diabetes mellitus (DM). Patient group included 50 asymptomatic children with type 1 DM, while 50 healthy matched children served as a control group. We reported that the cTnT I levels were significantly higher in diabetic children and were significantly positively correlated with HbA1c. Conventional echocardiography failed to show any systolic and diastolic dysfunction of the LV. 4D-LVEF (that reflected LV systolic function) as well as LV diastolic function by TDI were significantly impaired in diabetic children compared to the control group. Moreover, there was a significant decrease in all component of strain as detected by 3D STE in diabetic children and that decrease correlated well with 4D LV EF and control of DM but did not correlate with the duration of DM. From these data, we concluded that 3D-STE is considered an effective

tool for diagnosis of early LV dysfunction in asymptomatic children with type 1 DM [10].

Finally, we can conclude that early detection of diabetic cardiac dysfunction by cardiac biomarkers and recent advanced echocardiographic modalities is of great importance, because in early stages of diabetic cardiomyopathy, medical interventions by different cardio protective drugs could prevent or delay the progression and reduce the risk of development of heart failure in such patients.

There are several ongoing clinical trials and studies in our department for the evaluation of effectiveness of some cardioprotective drugs as zinc, statin, carnitine and captopril for the prevention of diabetic cardiomyopathy.

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