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Early Detection and Prevention of Diabetic Cardiomyopathy in Pediatric Age Group

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Abbreviations: DM: Diabetes Mellitus; CVD: Cardiovascular Disease; DCM: Diabetic Cardiomyopathy; TNF: Tumor Necrosis Factor; NF: Nuclear Factor; MDA: Malondialdhyde; MMPs Matrix Metalloproteinases; RT3DE: Real-Time Three-Dimensional Echocardiography; LV: Left Ventricle; TASE: Tricuspid Annular Systolic Excursion; MPI: Myocardial Performance Index; CBC Complete Blood Count; PP Postprandial; TDI: Tissue Doppler Imaging; MMP-2: Matrix Metalloproteinase-2

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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 multi-factorial 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-κB (NF-κB) which stimulates the production of inflammatory mediators (such as tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β)) [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-κB, which up-regulates several genes correlated to fibrosis, including transforming growth factor-β (TGF-β), in diabetic heart [7].

In previous study we proved that diabetic patients had significant lower level of glutathione and significant higher levels of malondialdhyde (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 were 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, antiapoptotic and antifibrotic properties that ALA showed in type 1 diabetic patient [8].

In another recherché we studied 30 children with type-1 diabetes mellitus as a patient group and 30 healthy children matched for age and sex as controls. It evaluated RV functions by tissue Doppler imaging, speckle tracking imaging, and real-time three-dimensional echocardiography (RT3DE), as well as assessing resistin serum level using enzyme-linked immunosorbent assay. The left ventricle (LV) showed no significant difference between the two groups in E/A ratio across the mitral valve, ejection fraction, and S wave mitral annulus. However, it showed significant decrease in the E′/A′ wave of mitral annulus, impairment of LV myocardial performance index (MPI), and decrease in LV EF measured by RT3DE in diabetic patients compared to the control group. Significant differences in the mean value of tricuspid annular systolic excursion (TASE), pulmonary artery pressure, longitudinal systolic strain (RV LSS), MPI, and RV ejection fraction were observed between the studied groups. Yet, no significant differences in E/A ratio and S value were observed between the two groups. Significant positive correlation of resistin level with age of studied group and significant negative correlation of resistin with both TASE and RV LSS values.

From these data we confirmed the presence of subclinical RV systolic and diastolic dysfunction in type-1 diabetic children with positive correlation between resistin level and RV dysfunction among children with type-1-diabetes mellitus [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). Fifty asymptomatic children with type 1 DM were included as a patient group. Fifty healthy children of matched age, sex, and weight served as a control group. Laboratory investigations in the form of complete blood count (CBC), liver function test, renal function test, complete blood lipid profile, glycosylated hemoglobin (HbA1c), fasting and 2 hours postprandial (PP) glucose levels, and cardiac troponin I (cTnT I) were drawn. Complete echocardiographic evaluation of the left ventricular (LV) function was performed in the form of conventional echo, 2D strain, tissue Doppler imaging (TDI), and 3D-STE.

We reported that the cTnT I levels were significantly higher in the patient group than the control group, and this increase was significantly correlated with Hb A1c. Conventional echocardiography showed normal systolic and diastolic function of the LV. Diastolic (by TDI) as well as systolic functions of LV (by 4D LV quantification tool) were found to be significantly lower in patient group than control group. 3D-STE examination showed that there was a significant decrease in all component of strain in patient group than control group and that decrease correlated well with 4D LV EF but did not correlate with the duration of DM. There was a significant negative correlation between longitudinal strain and the control of DM. From these data we concluded that 3D-STE is a good tool for prediction of early cardiac 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 individuals with diabetes mellitus.

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

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