Detection of diabetic cardiomyopathy in Egyptian children and adolescents with longstanding Type 1 diabetes and evaluating the effect of α-tocopherol supplementation on cardiac functions after 1 year; a single center prospective study.

Keywords
α-tocopherol, N-terminal prohormone of brain natriuretic peptide, Diabetic cardiomyopathy, Type 1 diabetes, Children and adolescents, Speckle tracking echocardiography

Abstract
Introduction
Diabetic cardiomyopathy (DCM) is a serious complication that frequently occurs in patients with type 1 diabetes (T1D) necessitating early diagnosis. The aim of the current study was to detect subclinical DCM in Egyptian children and adolescents with T1D and evaluate the effect of antioxidants on myocardial dysfunction.

Material and methods
The current prospective observational cohort study included 81 T1D patients (9-20 years old) with diabetes duration > 4 years compared to 50 age and sex matched non-diabetic controls. Serum N-terminal prohormone of brain natriuretic peptide (NT-proBNP) was assessed in addition to conventional echocardiography, tissue Doppler imaging (TDI) and speckle tracking echocardiography (STE). Patients with myocardial dysfunction were supplemented with vitamin E (α-tocopherol) as an antioxidant for 1 year, then follow up echocardiography was done.

Results
NT-proBNP was elevated in 73 (90.1%) patients, 50.6% had left ventricular (LV) diastolic dysfunction, 14.8% had right ventricular (RV) diastolic dysfunction, 84% had LV systolic dysfunction and 91.4% had RV systolic dysfunction with statistically significant difference compared to controls. There was a significant negative correlation between LV global longitudinal strain (GLS) and NT-proBNP ($p<0.001$, $r=-0.796$). ROC curve analysis showed that NT-proBNP at a cut-off point ≥ 195 ng/ml detected LV systolic dysfunction function with 89.7% sensitivity and 84.6% specificity. Follow up after one year of α-tocopherol supplementation revealed significant improvement in LV systolic and diastolic functions as well as RV systolic dysfunction.

Conclusions
NT-proBNP and non-conventional echocardiography were useful in early detection of subclinical cardiomyopathy in patients with T1D. Antioxidant treatment improved subclinical myocardial dysfunction in T1D patients.

Explanation letter
Response to reviewers' comments
Review 1:
The paper was improved, and the recommendations were addressed. Still, I consider that the Table 1b must be simplified, and all the normal data could be deleted:
chronic:
limited joint mobility ... 7 .... 8.6%

Preprint

neurogenic bladder ... 5 ... 6.2%
neuropathy ... 2 ... 2.5%
retinopathy ... 3 ... 3.7%
nephropathy ... 27 ... 33.3%

And the same for all lines, including thyroid and celiac screening. There is no need to include all "normal" lines, and in this way, the table would be simplified and better understood.

Response: Table 1b was simplified by removing all lines with normal values (in red).

Review 2:
Authors have chosen to analyze a very interesting subject in area of diabetes, heart failure and potentials for prevention. Although, a great effort by authors is really appreciated, the study design lacks multicentric approach, as well as on-treatment blind-folding of evaluated subjects, which seriously challenges potential for avoiding bias in obtained results. With aforementioned as a major comment, I DO NOT RECOMMEND this manuscript (AMS-13713-2021-02) in present form, to be accepted for publishing as a research paper in Archives of Medical Science.

Response: Unfortunately, the follow up of cases was not blinded as all cases with cardiomyopathy were given vitamin E to improve their myocardial dysfunction. We couldn't leave cases with myocardial dysfunction without medical intervention. This would have been unethical.

Cover letter (reviewers' response).docx

Preprint

Title page

Title of the paper:
Detection of diabetic cardiomyopathy in Egyptian children and adolescents with longstanding Type 1 diabetes and evaluating the effect of α-tocopherol supplementation on cardiac functions after 1 year; a single center prospective study

The institute where the work was conducted:
Diabetes, Endocrine and Metabolism Pediatric Unit, Children hospital, Cairo University

Corresponding author:
Noha Musa
Assistant professor of Pediatric Endocrinology, Cairo University
Work address: Diabetes, Endocrine and Metabolism Pediatric Unit, Cairo University, Cairo, Egypt
Home address: 15 Naser El Thawra street, Haram, Giza
Email: noha.musa@yahoo.com
Phone no: +2 01225304041
Postal code: 12111
ORCID ID: 0000-0002-1036-9755

Running head:
α-tocopherol in diabetic cardiomyopathy

Preprint

Structured Abstract

Background: Diabetic cardiomyopathy (DCM) is a serious complication that frequently occurs in patients with type 1 diabetes (T1D) necessitating early diagnosis. The aim of the current study was to detect subclinical DCM in Egyptian children and adolescents with T1D and evaluate the effect of antioxidants on myocardial dysfunction. **Methods:** The current prospective observational cohort study included 81 T1D patients (9-20 years old) with diabetes duration > 4 years duration compared to 50 age and sex matched non-diabetic controls. Serum N-terminal prohormone of brain natriuretic peptide (NT-proBNP) was assessed in addition to conventional echocardiography, tissue Doppler imaging (TDI) and speckle tracking echocardiography (STE). Patients with myocardial dysfunction were supplemented with vitamin E (α-tocopherol) as an antioxidant for 1 year, then follow up echocardiography was done. **Results:** NT-proBNP was elevated in 73 (90.1%) patients, 50.6% had left ventricular (LV) diastolic dysfunction, 14.8% had right ventricular (RV) diastolic dysfunction, 84% had LV systolic dysfunction and 91.4% had RV systolic dysfunction with statistically significant difference compared to non-diabetic controls. There was a significant negative correlation between LV global longitudinal strain (GLS) and NT-proBNP ($p<0.001$, $r=-0.796$). ROC curve analysis showed that NT-proBNP at a cut-off point ≥ 195 ng/ml detected LV systolic dysfunction function with 89.7% sensitivity and 84.6% specificity. Follow up after one year of α-tocopherol supplementation revealed significant improvement in LV systolic and diastolic functions as well as RV systolic dysfunction. **Conclusion:** NT-proBNP and non-conventional echocardiography were useful in early detection of subclinical cardiomyopathy in patients with T1D. Antioxidant treatment improved subclinical myocardial dysfunction in T1D patients.

Keywords: Type 1 diabetes; Children and adolescents; Diabetic cardiomyopathy; N-terminal prohormone of brain natriuretic peptide; Speckle tracking echocardiography; α-tocopherol

Preprint

Introduction:

Diabetic cardiomyopathy (DCM) is defined as a ventricular dysfunction in diabetic patients, independently of coronary artery disease, valve disease or hypertension [1] affecting approximately 12% of patients with diabetes [2]. It is an advanced left ventricular (LV) diastolic dysfunction characterized by an intermediate stage between impaired relaxation and restrictive filling with reduced myocardial contractility and strain [3]. The pathogenesis of DCM is complicated with no precise specific mechanisms [1]. Nowadays, the minimal criteria to diagnose DCM include LV diastolic dysfunction and/or reduced LV ejection fraction (EF), pathological LV hypertrophy, and interstitial fibrosis [4]. Definitive diagnosis of DCM can be established by endomyocardial biopsy [5] or by cardiac catheterization [6]. However, these techniques are invasive, hence the need for developing new non-invasive yet accurate techniques for early diagnosis of DCM. Echocardiography is the gold standard diagnostic tool to identify structural cardiac disorders especially being non-invasive [1] with speckle tracking echocardiography (STE) being a technique that overcomes major drawbacks of conventional echocardiography [7]. Detection of different biomarkers of myocardial damage might be optimal for DCM diagnosis. Natriuretic peptides and their biologically inactive fragment N-terminal prohormone of brain natriuretic peptide (NT-proBNP) are considered to be pro-hypertrophic factors for DCM thus; their premature detection could be helpful for early diagnosis of DCM [3].

Currently, no effective specific treatment is available for DCM except for controlling blood glucose and lipid abnormalities as well as treatment of heart failure symptoms [1]. Many studies have been conducted to demonstrate the protective or therapeutic effects of antioxidants on the cardiomyocytes [8]; some of them showed promising results [9,10]. Vitamin E is the most prevalent naturally occurring antioxidant and has been shown to retard atherosclerosis. It also reduces the cytotoxic effect of oxidized lipoproteins, smooth muscle cell proliferation, platelet adherence and aggregation, and inflammation, and improves endothelial function [11]. Vitamin E was also proposed for the prevention of microvascular complications of diabetes as it decreased hyperglycemia-induced protein kinase C (PKC) activation and d-acetyl-glycerol (DAG) levels, associated with abnormalities in the retinal, renal, and vascular tissues in diabetes [12].

Preprint

The aim of the current study was to detect subclinical DCM in children and adolescents with longstanding T1D using plasma NT-pro-BNP and echocardiography and to assess the effectiveness of oral Vitamin (E) as an antioxidant for treatment of DCM and prevention of disease progression.

Materials and Methods:

Study population

This prospective cohort study included 81 children and adolescents (9-20 years old) with T1D according to ISPAD 2018 criteria for diagnosis of diabetes (Hb1Ac > 6.5% and fasting glucose > 126 mg/dl {7 mmol/l}) with low C-peptide and positive pancreatic autoantibodies. Patients with type-2 diabetes or monogenic diabetes, congenital heart diseases or arrhythmias, acute or chronic systemic disease that can affect cardiac function (i.e., hypertension, renal failure) and patients under medications known to affect cardiac physiology (i.e., beta blockers, antiarrhythmic) were excluded from the study. Patients were recruited from Diabetes, Endocrine and Metabolism Pediatric Unit, Cairo University during the period from June 2017 till March 2019. Fifty non-diabetic age and sex matched healthy children and adolescents were studied as controls regarding cardiac biomarkers and echocardiography.

The study protocol was approved by the Research Ethics Committee of Cairo University Hospitals (approval date: 20/12/2017, approval number: I-200317) and informed consents were obtained from participant's legal guardians before enrollment. The study was carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki).

Patients were subjected to clinical history taking including age, sex, onset of diabetes, diabetes duration, daily insulin requirements and family history. Physical examination included blood pressure (BP) assessment (using mercury sphygmomanometer at 3 different times within 2 weeks), which was plotted on the Egyptian BP curves [13] in addition to pubertal staging [14]. Anthropometric data (weight, height, waist circumference) were performed with calculation of body mass index (BMI) as body weight (kg)/height (m2), height and weight standard deviation score (SDS), then results were plotted on the Egyptian growth curves [15]. Biochemical assessment for NT-proBNP was performed; sample collection was performed via

Preprint

aseptic venipuncture, 2 ml of blood was taken in plastic tubes containing EDTA and then immediately placed on ice and centrifuged at 2500 rpm for 20 minutes and serum was harvested and kept at -80°C till analysis date. NT-proBNP was measured by enzyme linked immunosorbent assay (ELISA). We used cut-off value of >125 pg/ml to define high risk NT-proBNP [16].

Mean values for glycosylated hemoglobin (HbA1c), total cholesterol (TC), triglycerides (TG), Low-density Lipoprotein Cholesterol (LDL-C) and High-density Lipoprotein Cholesterol (HDL-C), thyroid profile (free T4 and TSH) and urinary albumin creatinine ratio (uACR) over the previous 3 years were collected from the patients' medical records. Dyslipidaemia was defined with TC ≥ 200 mg/dl (hypercholesterolemia), TG ≥130 mg/dl (hypertriglyceridemia), LDL ≥ 130 mg /dl (high LDL), HDL < 35 mg/dl (high risk HDL) [17]. The presence of microalbuminuria or macro-albuminuria was diagnosed when uACR was 30-299 mg/g or ≥ 300 mg/g respectively. Glycemic control was classified according to ISPAD 2018 guidelines [18].

Echocardiography was performed initially and after 1 year by an experienced pediatric cardiologist and by using conventional trans-thoracic two-dimensional (2D) Echo/Doppler (M mode) and Tissue Doppler Imaging (TDI) as well as speckle tracking echocardiography (STE). By 2D-Echo/Doppler, M-mode measurements were done at the tips of the mitral valve leaflets in the parasternal long axis view. Left ventricular (LV) dimensions were examined in systole and diastole, and then, fractional shortening (FS) and ejection fraction (EF) were estimated. Also, LV end-diastolic volume index (LVEDVI) was calculated by dividing left ventricular end diastolic volume between body surface area. By TDI, the early filling (E) and early diastolic mitral annular velocity (E') ratio (E/E') was assessed at the mid-oesophageal four-chambers view with the pulsed-wave Doppler in basal segments of the LV lateral wall and septal wall for early detection of diastolic LV dysfunction. Global longitudinal strain (GLS) was calculated from the 17 myocardial segments at end-systole. For RV diastolic function, the early filling (E) and late diastolic tricuspid annular velocity (A') ratio (E/A') of the basal segments of the RV free wall was estimated.

Impaired results were defined as FS<28%, EF <55%, GLS <20%, Tricuspid annular E'/A' <1 (RV systolic dysfunction), Left ventricular e/è >6 (LV diastolic dysfunction) [19].

Preprint

Intervention

Patients with positive echocardiographic findings were given Vitamin (E) as an antioxidant (dose 600 IU/day) for a duration of 1 year then their myocardial functions were reassessed by STE (32 cases adhered strictly to the medications and follow up; completed the study).

Statistical analysis

Statistical analyses were performed using the statistical package for social science "SPSS" version. Associations between qualitative variables were studied by the Chi-square test, or by the Fisher's exact test in those cases in which the approximation to the Chi-square distribution was not appropriated. Quantitative variables were summarized by mean and standard deviation, or by median and interquartile range, depending on the symmetry of the data distribution. Qualitative variables were included as absolute and relative frequencies. Variables with normal distribution were compared using Student's t test, while variables with non-normal distribution were compared using the Mann Whitney U test. Associations between quantitative variables were studied by the Pearson's correlation coefficient. In order to identify potential predictors for ventricular diastolic dysfunction, logistic regression models and ROC curves were used. ROC curves showed the area under the curve with its 95% confidence interval 8 and the cut-off point obtained by Youden's criterion, with respective sensitivity and specificity values. P values less than 0.05 were significant.

Preprint

Results:

The study included 81 cases (38.3 % were males, 61.7% were females) with a mean age of 14.6 ± 2.4 years, mean age of diabetes onset of 6.4 ± 2.8 years and mean diabetes duration of 8 ± 2.8 years. Demographic, clinical and laboratory data of the study group are shown in Table 1a,1b. The whole study group experienced no cardiac symptoms. Mean serum NT-proBNP was 470.1 ± 362.6 pg/ml with elevated proBNP levels in 73 (90.1%) cases. Regarding echocardiography, 50.6% had LV diastolic dysfunction (TDI LV E/E' > 8), 84% had LV systolic dysfunction (GLS-LV ≤ 18), 14.8% had RV diastolic dysfunction (TDI Tricuspid E'/A' ratio <1) and 91.4% had RV systolic dysfunction (GLS-RV ≤ 18) with statistically

significant difference between cases and non-diabetic controls (p<0.001). Statistically significant difference was detected between cases and non-diabetic controls regarding NT-proBNP, TDI LV E/E', GLS-LV and GLS-RV (p <0.001) [Table 2].

Regarding correlation studies [Table 3], NT-proBNP correlated directly with duration of diabetes (r= 0.221, p=0.048) and weight SDS (r=0.223, p=0.013). However, it correlated inversely with GLS-LV (p<0.001, r=-0.796). A significant positive correlation was found between TDI LVE/E' and duration of diabetes, frequency of DKA, DBP, FBG, HbA1c as well as TC (p=0.015, 0.012, 0.008, 0.013, 0.03 and 0.023 respectively). Tricuspid E'/A' correlated inversely with long-acting insulin requirements, LDL, TGs and serum creatinine with a p value of 0.05, 0.023, 0.041 and 0.023 respectively. There was a significant negative correlation between GLS-LV and NT-proBNP (i.e. the higher the NT-proBNP levels the worse the LV systolic functions; p <0.001) as well as duration of diabetes, SBP & TGs (p= 0.05, 0.023 & 0.015 respectively), while a significant negative correlation was detected between GLS-RV and uACR (r=-0.22, p=0.049). LVEDVI had a statistically significant inverse correlation with DBP (p= 0.014), whereas FS had a statistically significant direct correlation with the SBP (r=0.221, p=0.047). There was significant difference between males and females regarding FS and EF (p= 0.045 & 0.039 respectively). Multivariate analysis showed that the best predictor of LV diastolic dysfunction was the number of DKA episodes since onset of diabetes (p=0.047), the best predictor of RV diastolic dysfunction was LDL (p=0.041), the best predictor of RV systolic dysfunction was uACR (p=0.049). ROC curve analysis showed that NT-proBNP had the ability to detect LV systolic dysfunction function at a cut-off point of ≥ 195 pg/ml with 89.7% sensitivity and 84.6% specificity [Fig. 1].

Follow up of cases after Vitamin E supplementation for one year revealed that the mean LV E/E', GLS-LV and GLS-RV improved significantly (p <0.001) (i.e. improved LV diastolic dysfunction as well as LV and RV systolic dysfunction) [Fig. 2].

Discussion:

Previous reports showed that quantification of NT-proBNP combined with 2D-Echo-Doppler imaging

Preprint

was more reliable to diagnose DCM in type 2 diabetes mellitus (T2DM) patients than any of them alone [20]. In the current study, 73 (90.1%) patients had high NT-proBNP indicating high prevalence of DCM among children with T1D. Ponikowski et al. (2016) found that NT-proBNP concentrations ≤125 pg/mL in the non-acute setting and <300 pg/mL in the acute setting ruled out suspected HF with a high negative predictive value of 94% and 98% respectively [21]. Epshteyn et al. (2003) reported that in patients with T1D, high NT-proBNP could identify LV systolic dysfunction in 96% of cases [22]. Other studies demonstrated elevated NT-proBNP in uncontrolled patients with diabetes but not in asymptomatic patients with mild diastolic dysfunction [23]. In the current study, a cutoff point of ≥ 195 pg/ml for NT-proBNP was able to detect LV systolic dysfunction. On the other hand, Salem et al. (2009) showed that the NT-proBNP was elevated in diabetics with best cut-off value of 62.5 pg/mL with sensitivity 82% and specificity 95% for detection of isolated diastolic dysfunction [24].

Our results showed that LV E/E' "indicator of the LV diastolic dysfunction" was significantly higher than controls denoting the presence of LV diastolic dysfunction in T1D adolescents. Similar results were obtained by Bradley et al. (2018) who showed statistically significant difference in LV E/E' between diabetic and healthy groups (p=0.0003) [25]. On the contrary, Abd-El Aziz et al. (2017) reported no statistically significant difference between diabetic and healthy groups (p=0.425) [26]. In this work, we found significant positive correlations between LV E/E' and duration of diabetes, average DBP, frequency of DKA episodes, TC, FBG as well as HbA1. Association between early diastolic dysfunction and poor metabolic control (high HbA1c) and duration of T1D was reported in some studies [24,27,28] while other studies failed to show such association [26, 29,30].

As regards Tricuspid E'/A' "indicator of RV diastolic dysfunction" in our study, no statistically significant difference was found between cases and non-diabetic controls. Similar results were reported by Abd-El Aziz et al. (2017) [26] indicating that the RV diastolic dysfunction is not frequently associated with DCM as LV diastolic dysfunction. In the current study, the incidence of RV diastolic dysfunction (Tricuspid E'/A' <1) was 14.8 % and this was very close to the incidence of RV diastolic dysfunction reported by Ahmed et al. (2018) who found that 13.9% of patients had impaired diastolic function [31].

Preprint

Our results showed a significant negative correlation between Tricuspid E'/A' and long-acting daily insulin requirements, LDL, TGs and creatinine. Similar results were reported by Abd-El Aziz et al. (2017) as they observed that patients with dyslipidemia had worse RV diastolic functions [26]. Elevated serum creatinine was associated with a higher risk of cardiorenal events and death as observed by Collard et al. (2018) [32].

Multivariate analysis showed that the number of DKA episodes since the onset of diabetes was the best predictor of LV diastolic dysfunction, while LDL was the best predictor of RV diastolic dysfunction. Severe DKA initiates synthesis of antibodies to cardiac self-antigens that are involved in the early immunopathogenesis of DCM in young patients with T1D as explained by Hoffman et al. (2015) who reported significant rise in those antibodies during DKA and its treatment [33]. Diabetes is usually associated with higher concentrations of modified forms of LDL particles such as oxidized LDL, glycosylated LDL and electronegative LDL which have potential negative effects on cardiomyocyte function [34].

As for GLS-LV "indicator of LV systolic dysfunction", a statistically significant difference was found between cases and non-diabetic controls indicating high prevalence of LV systolic dysfunction among the diabetes group, despite normal EF. Our results came similar to several studies [35,36,37]. In the current study, the prevalence of LV systolic dysfunction (GLS-LV $\leq$ 18) was about 84 %, that was higher than Mochizuki et al. (2015) who detected prevalence of 37% [38]. This could be attributed to the patients' selection criteria as they included 150 patients of both T1D and T2D with lower HbA1c (8.2% versus 9.9% in our study group).

In the current study, we found a significant negative correlation between GLS-LV and NT-proBNP. A statistically significant direct correlation was reported between the LV-GLS and duration of diabetes that came in agreement with several studies [35,39] but disagreed with others [40,36,41]. The current study showed no association between poor glycemic control (i.e. HbA1C) and LV systolic dysfunction in contrast to Labombarda el al. (2014); Altun et al. (2016) and Hensel et al. (2016) [40,36,41].

Concerning GLS-RV "indicator of RV systolic dysfunction", a statistically significant difference was

Preprint

found between cases and non-diabetic controls in the current study. Similar results were reported by Ahmed et al. (2018) who found impaired RV-GLS significantly in the patients compared to controls [31]. In the current work, the incidence of RV systolic dysfunction (GLS-RV ≤ 18) was 91.4 %, that came similar to Ahmed et al. (2018) who reported a prevalence of 85% [31]. RV involvement in diabetes could be attributed to several factors as hyperinsulinemia causing RV hypertrophy, hyperglycemia resulting in myocardial deposition of advanced glycosylation products, hyperlipidemia causing myocardial steatosis, and diabetes-associated inflammatory state [42]. Diabetic LV cardiomyopathy can affect the RV through affecting the ventricular septum or increasing the RV afterload which in turn could lead to hypertrophy and fibrosis [43]. There was a significant negative correlation between GLS-RV and mean uACR which was the best predictor of RV systolic dysfunction in multivariate regression analysis. This came consistent with Enomoto et al. (2016) who found a significant association between the GLS and nephropathy stage in patients with T2D [44].

There was no significant correlation between HbA1c and indices of myocardial dysfunction except for LV E/E' Average (LV diastolic dysfunction) which might be attributed to the fact that microvascular and macrovascular complications in patients with DM are mainly dependent on two major components of glycemic abnormalities: chronic sustained hyperglycemia and acute glycemic fluctuations from high (peaks) to low (nadirs) values and vice versa (glycemic variability) [45].

Endothelial dysfunction due to hyperglycemia-induced oxidative damage is considered an important predictor of future cardiovascular risk in patients with T1D. Many studies involved patients with T2D aiming to evaluate the effectiveness of antioxidant vitamins or micronutrients in controlling the cardiovascular morbidities associated with diabetes [46,47,48]. Fucoxanthin protected cardiomyocytes and attenuated high glucose-mediated oxidative stress in rat models [49]. Balbi et al (2018) conducted a meta-analysis of 12 randomized control trials to evaluate the antioxidant effects of vitamins in T2D (main antioxidants studied were vitamins B, C, D and E). Vitamin E was related to significant reduction of blood glucose and HbA1c compared to placebo as well as enhancing the total antioxidant capacity [9]. A systematic review aiming to evaluate the impact of micronutrients in the development of cardiovascular

Preprint

outcomes in patients with diabetes showed that high levels of α-tocopherol in serum were associated with 30% lower coronary artery disease (CAD) risk [50]. As regards T1D, fewer studies were performed to evaluate the usefulness of Vit E. Gupta et al. (2011) reported that that Vitamin E supplementation for 3 months (dose of 600 IU/day) was associated with reduced oxidative stress in T1D patients and improved antioxidant defense system [51]. Cazeau et al. (2016) studied the effect of combined treatment with the antioxidant vitamins C and E on endothelial function in two males and 7 females and noticed no differences in endothelial functions neither total antioxidant capacity [10]. Those negative results might be due to the very short course (6 weeks only) supplementation of Vitamins C and E. However, our results showed α-tocopherol treatment for one year made significant improvement in LV systolic and diastolic functions as well as RV systolic function. This might highlight the importance of vitamin E as a novel, cheap, readily available and effective therapy for management of DCM.

Study limitations included small sample size and loss of cases during follow up period, while strengths of the study included the use of non-conventional echocardiography techniques (speckled tracking echocardiograpy) that have high sensitivity in detecting early myocardial changes rather than the conventional echocardiography and also the intervention of supplementing vitamin E to the children with DCM and monitoring its effect on myocardial dysfunction which was not assessed in pediatric population before.

Conclusion:

DCM was prevalent in Egyptian children and adolescents with longstanding T1D. NT-proBNP and non-conventional echocardiography were useful in early detection of subclinical cardiomyopathy in patients with T1D. Antioxidant treatment improved subclinical myocardial dysfunction in T1D patients.

Acknowledgements:

Doctors and nurses in Diabetes, Endocrine and Metabolism Pediatric Unit, Cairo University. We also acknowledge the patients and their parents for their participation in the study.

Preprint

Declarations of interest: Authors have no conflict of interest to declare.

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Compliance with Ethical Standards: All procedures performed in studies involving human participants were in accordance with the ethical standards of Cairo University and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from every individual participant included in the study or his legal guardians.

Preprint

References

[1] Ma C, Luo H, Liu B et al. Long noncoding RNAs: A new player in the prevention and treatment of diabetic cardiomyopathy? Diabetes Metab Res Rev. 2018 Nov; 34(8):e3056.

[2] Trachanas K, Sideris S, Aggeli C et al. Diabetic cardiomyopathy: from pathophysiology to treatment. Hellenic J Cardiol. 2014; 55(5): 411–21

[3] Lorenzo-Almoros A, Tunon J, Orejas M et al. Diagnostic approaches for diabetic cardiomyopathy. Cardiovas Diabetol. 2017;16(1):28

[4] Fontes-Carvalho R, Ladeiras-Lopes R, Bettencourt P et al. Diastolic dysfunction in the diabetic continuum: association with insulin resistance, metabolic syndrome and type 2 diabetes. Cardiovasc Diabetol. 2015; 14:4

[5] Gil KE, Pawlak A, Gil RJ et al. The role of invasive diagnostics and its impact on the treatment of dilated cardiomyopathy: a systematic review. Adv Med Sci. 2016 Sep;61(2):331-343

[6] Zile MR, Baicu CF, Gaasch WH. Diastolic heart failure–abnormalities in active relaxation and passive stiffness of the left ventricle. N Engl J Med. 2004; 350(19):1953–9.

[7] Wang J, Khoury DS, Yue Y et al. Preserved left ventricular twist and circumferential deformation, but depressed longitudinal and radial deformation in patients with diastolic heart failure. Eur Heart J. 2008; 29(10):1283–9.

[8] Yan B, Ren J, Zhang Q et al. Antioxidative Effects of Natural Products on Diabetic Cardiomyopathy. J Diabetes Res. 2017;2017:2070178. doi:10.1155/2017/2070178

[9] Balbi ME, Tonin FS, Mendes AM et al. Antioxidant effects of vitamins in type 2 diabetes: a meta-analysis of randomized controlled trials. Diabetol Metab Syndr. 2018 Mar 14;10:18. doi: 10.1186/s13098-018-0318-5

[10] Cazeau RM, Huang H, Bauer JA, Hoffman RB. Effect of Vitamins C and E on Endothelial Function in Type 1 Diabetes Mellitus. J Diabetes Res. 2016;2016:3271293

[11] Andrew R, Skyrme-Jones P, O'Brien RC et al. Vitamin E supplementation improves endothelial function in type I diabetes mellitus: a randomized, placebo-controlled study. J Am Coll Cardiol. 2000;

Preprint

36:94–102

[12] Bursell S-E, King GL. Can protein kinase C inhibition and vitamin E prevent the development of diabetic vascular complications? Diabetes Res Clin Pract. 1999; 45*:*169–182

[13] El-shafie AM, El-Gendy FM, Allhony DM et al. Establishment of blood pressure nomograms representative for Egyptian children and adolescents: a cross-sectional study. BMJ Open. 2018 Jul 25;8(7): e020609. doi: 10.1136/bmjopen-2017-020609

[14] Tanner JM. Growth at adolescence, ed 2, Oxford, Blackwell Scientific; 1962.

[15] Ghali I, Salah N, Hussien F et al. Egyptian growth curves for infants, children and adolescents. In: Satorio A, Buckler JMH, Marazzi N, editors. Crecere nel mondo. Italy: Ferring Publisher 2008; 2002.

[16] Januzzi JL, van Kimmenade R, Lainchbury J et al. NT-proBNP Testing for Diagnosis and Short-Term Prognosis in Acute Destabilized Heart Failure: An International Pooled Analysis of 1256 Patients: The International Collaborative of NT-proBNP Study. Eur Heart J. 2006; 27:330 –337

[17] Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents; National Heart, Lung, and Blood Institute. Expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents: summary report. Pediatrics. 2011;128 (5):S213-S256.

[18] DiMeglio LA, Acerini CL, Codner E et al. ISPAD Clinical Practice Consensus Guidelines 2018: Glycemic control targets and glucose monitoring for children, adolescents, and young adults with diabetes. Pediatr Diabetes. 2018;19(27):105–114

[19] Tissot C, Singh Y, Sekarski N. Echocardiographic Evaluation of Ventricular Function-For the Neonatologist and Pediatric Intensivist. Front Pediatr. 2018;6:79.

[20] Betti I, Castelli G, Barchielli A et al. The role of N-terminal PRO-brain natriuretic peptide and echocardiography for screening asymptomatic left ventricular dysfunction in a population at high risk for heart failure. The PROBE-HF study. J Card Fail. 2009; 15(5):377–84.

[21] Ponikowski P, Voors AA, Anker SD et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart

Preprint

failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2016; 37(27): 2129–2200.

[22] Epshteyn V, Morrison K, Krishnaswamy P et al. Utility of B-type natriuretic peptide (BNP) as a screen for left ventricular dysfunction in patients with diabetes. Diabetes Care. 2003; 26(7):2081–7.

[23] Dencker M, Stagmo M, Dorkhan M. Relationship between natriuretic peptides and echocardiography parameters in patients with poorly regulated type 2 diabetes. Vasc Health Risk Manag. 2010; 6:373–82.

[24] Salem M, El Behery S, Adly A et al. Early predictors of myocardial disease in children and adolescents with type 1 diabetes mellitus. Pediatr Diabetes. 2009: 10(8): 513–521.

[25] Bradley TJ, Slorach C, Mahmud FH et al. Early changes in cardiovascular structure and function in adolescents with type 1. Cardiovasc Diabetol. 2016 Feb 16;15:31. doi: 10.1186/s12933-016-0351-3.

[26] Abd-El Aziz FM, Abdelghaffar S, Hussien ME, Fattouh AM. Evaluation of Cardiac Functions in Children and Adolescents with Type 1 diabetes. J Cardiovasc Ultrasound. 2017;25(1):12-19

[27] Vazeou A, Papadopoulou A, Miha M et al. Cardiovascular impairment in children, adolescents, and young adults with type 1 diabetes mellitus (T1DM). Eur J Pediatr. 2008;167(8):877–884.

[28] Kim EH, Kim YH. Left-ventricular function in children and adolescents with type 1 diabetes mellitus. Korean Circ J. 2010;40(3):125–130.

[29] Elshahed GS, Ahmed MI, El-Beblawy NS et al. Evaluation of right and LV systolic and diastolic function in patients with type I diabetes using echocardiography and tissue Doppler imaging. Suez Canal Univ Med J. 2008;11:65–74.

[30] Brunvand L, Fugelseth D, Stensaeth KH et al. Early reduced myocardial diastolic function in children and adolescents with type 1 diabetes mellitus a population-based study. BMC Cardiovasc Disord. 2016; 16:103

[31] Ahmed TA, Ahmed YA, Arafa AI, Salah RA. Detection of occult right ventricular dysfunction in young Egyptians with type 1 diabetes mellitus by two-dimensional speckle tracking echocardiography. Indian Heart J. 2018;70(5):665–671.

Preprint

[32] Collard D, Brouwer TF, Peters RJ et al. Creatinine Rise during Blood Pressure Therapy and the Risk of Adverse Clinical Outcomes in Patients with Type 2 Diabetes Mellitus. A Post Hoc Analysis of the ACCORD-BP Randomized Controlled Trial. Hypertension. 2018;72(6):1337-1344

[33] Hoffman WH, Sharma M, Cihakova D et al. Cardiac antibody production to self-antigens in children and adolescents during and following the correction of severe diabetic ketoacidosis. Autoimmunity. 2016;49(3):188-96.

[34] Alonso N, Moliner P, Mauricio D. Pathogenesis, Clinical Features and Treatment of Diabetic Cardiomyopathy. Adv Exp Med Biol. 2018;1067:197-217.

[35] Yoldaş T, Örün UA, Sagsak E et al. Subclinical left ventricular systolic and diastolic dysfunction in type 1 diabetic children and adolescents with good metabolic control. Echocardiography. 2018 Feb;35(2):227-233.

[36] Altun G, Babaoglu K, Binnetoglu K et al. Subclinical left ventricular longitudinal and radial systolic dysfunction in children and adolescents with type 1 diabetes mellitus. Echocardiography. 2016;33(7): 1032–1039

[37] Jędrzejewska I, Król W, Światowiec A et al. Left and right ventricular systolic function impairment in type 1 diabetic young adults assessed by 2D speckle tracking echocardiography. Eur Heart J Cardiovasc Imaging.2016; 17:438–46.

[38] Mochizuki Y, Tanaka H, Matsumoto K et al. Association of peripheral nerve conduction in diabetic neuropathy with subclinical left ventricular systolic dysfunction. Cardiovasc Diabetol. 2015; 14:47 (1-9)

[39] Nakai H, Takeuchi M, Nishikage T et al. Subclinical left ventricular dysfunction in asymptomatic diabetic patients assessed by two-dimensional speckle tracking echocardiography: correlation with diabetic duration. Eur J Echocardiogr. 2009 Dec; 10(8):926-32.

[40] Labombarda F, Leport M, Morello R et al. Longitudinal left ventricular strain impairment in type 1 diabetes children and adolescents: a 2D speckle strain imaging study. Diabetes Metab. 2014;40(4):292–298

[41] Hensel KO, Grimmer F, Roskopf M et al. Subclinical alterations of cardiac mechanics present early in the course of pediatric type 1 diabetes mellitus: a prospective blinded speckle tracking stress

Preprint

echocardiography study. J Diabetes Res. 2016; 2016: 2583747.

[42] Tadic M, Celic V, Cuspidi C et al. Right heart mechanics in untreated normotensive patients with prediabetes and type 2 diabetes mellitus: a two- and three-dimensional echocardiographic study. J Am Soc Echocardiogr 2015;28(3):317-27.

[43] Pai RG. Right Ventricular Function Measures as Biomarkers of Diabetic Cardiomyopathy. J Am Soc Echocardiogr. 2015 Mar;28(3):328-9

[44] Enomoto M, Ishizu T, Seo Y et al. Myocardial dysfunction identified by three-dimensional speckle tracking echocardiography in type 2 diabetes patients relates to complications of microangiopathy. J Cardiol. 2016 Oct;68(4):282-287

[45] Nusca A, Tuccinardi D, Albano M et al. Glycemic variability in the development of cardiovascular complications in diabetes. Diabetes Metab Res Rev. 2018 Nov;34(8):e3047

[46] Ashor AW, Siervo M, Lara J et al. Effect of vitamin C and vitamin E supplementation on endothelial function: a systematic review and meta-analysis of randomised controlled trials. Br J Nutr. 2015;113(8):1182–94

[47] Montero D, Walther G, Stehouwer CD et al. Effect of antioxidant vitamin supplementation on endothelial function in type 2 diabetes mellitus: a systematic review and meta-analysis of randomized controlled trials. Obes Rev. 2014;15(2):107–16.

[48] Xu R, Zhang S, Tao A et al. Influence of vitamin E supplementation on glycaemic control: a meta-analysis of randomised controlled trials. PLoS ONE. 2014;9(4):e95008.

[49] Li F, Lei C. Fucoxanthin protects neonatal rat cardiomyocytes and attenuates high glucose-mediated oxidative stress via the AMPK pathway. Arc Med Sci. 2020. doi:10.5114/aoms.2020.94432.

[50] Sarmento RA, Silva FM, Sbruzzi G et al. Antioxidant micronutrients and cardiovascular risk in patients with diabetes: a systematic review. Arq Bras Cardiol. 2013 Sep;101(3):240-8.

[51] Gupta S1, Sharma TK, Kaushik GG, Shekhawat VP. Vitamin E supplementation may ameliorate oxidative stress in type 1 diabetes mellitus patients. Clin Lab. 2011;57(5-6):379-86

Preprint

Figure Legends:

Fig. 1. ROC curve analysis showing the discriminate ability of NT-proBNP in diagnosing LV systolic dysfunction

Fig. 2. Effect of vitamin E supplementation for 1 year on echocardiographic findings

Preprint

Table 1a: Demographic, clinical, biochemical and echocardiographic parameters of the study group

		Mean+SD/Median (IQR)*
Age (years)		14.6 ± 2.4
Age at onset of diabetes (years)		6.4 ± 2.8
Duration of diabetes (years)		8 ± 2.8
Total Insulin requirements (IU/kg/day)		1.2 ± 0.4
Basal insulin requirements (IU /kg/day)		0.5 ± 0.2
Bolus insulin requirements (IU/kg/day)		0.7 ± 0.3
Average number of DKA episodes/ year		1.5 (1 - 3)*
Clinical data		
Weight SDS		-0.2 (-0.8 - 0.9)*
Height SDS		-0.8 (-1.5 - 0.1)*
BMI (kg/m^2)		20.9 ± 3.4
BMI SDS		0.6 (-0.2 - 1.2)*
Waist circumference (cm)		71.3 ± 8.2
SBP (mmHg)		114.9 ± 9.5
DBP (mmHg)		76.2 ± 8.4
Biochemical analysis		
#HbA1c (%)		9.4 ± 1.7
#TC (mg/dl)		169.9 ± 32.7
#LDL (mg/dl)		101.1 ± 28.1
#HDL (mg/dl)		49.9 ± 11.9
#TGs (mg/dl)		87.4 ± 33.9
#uACR (mg/g)		20 (15 - 36)*
Creatinine (mg/dl)		0.7 ± 0.2
NT-proBNP (pg/ml)		470.1 ± 362.6
Echocardiography		
M-Mode	**FS %**	40.5 ± 5.5
	EF %	74 ± 8.3
TDI	**LV E/E'**	10.3 ± 4.2
	Tricuspid E'/A'	1.6 ± 0.5
STE	**GLS-LV**	13.9 ± 4.3
	GLS-RV	12.4 ± 3.9

DKA: diabetic ketoacidosis, **BMI**: body mass index, **SBP**: systolic blood pressure**, DBP**: diastolic blood pressure **SD:** standard deviation, **TC:** total cholesterol**, HDL:** High density lipoprotein, **LDL:** Low density lipoprotein, **TGs:** triglycerides, **HbA1c:** glycosylated hemoglobin, u**ACR:** urinary albumin creatinine ratio, **NT-proBNP**: N-terminal pro b-type natriuretic peptide, **TDI**: tissue doppler imaging, **STE:** speckled tracking echocardiography, **E'**: Early diastolic tissue velocity, **A'**: Atrial late diastolic tissue velocity, LV: left ventricular, **e/è:** early mitral inflow velocity / average of the early diastolic tissue velocities of septal and lateral walls, **GLS:** global longitudinal strain, **EF:** ejection fraction, **FS:** fractional shortening, **LV:** left ventricle, **RV:** right ventricle

Mean values of previous 3 years.

*Values expressed in median and interquartile range

Preprint

Table 1b: Demographic, clinical, biochemical and echocardiographic parameters of the study group

			Frequency	Percentage
Sex		**Males**	31	38.3 %
		Females	50	61.7 %
Exercise frequency		**Inactive**	23	28.4%
		Irregular	11	13.6%
		1-3 times / week	18	22.2%
		Daily	29	35.8%
Complications of diabetes				
Chronic	**Limited Joint Mobility**		7	8.6%
	Neurogenic bladder		5	6.2%
	Neuropathy		2	2.5%
	Retinopathy		3	3.7%
	Nephropathy		27	33.3%
Acute	**DKA**		58	71.6%
	Nocturnal Hypoglycemia		50	61.7%
	Nocturnal Hypoglycemia level (mg/dl)	**<40 mg/dl**	30	37%
		<70 md/dl	20	24.7%
Family History				
Diabetes (both type 1 or type 2)			44	54.3%
Hypertension			32	39.5%
Cardiovascular diseases			7	8.6%
Obesity			11	13.6%
Clinical data				
Weight SDS		**< -2 SDS**	3	3.7%
		-2 SDS - + 2S DS	72	88.9%
		> +2 SDS	6	7.4%
Height SDS		**< -2 SDS**	14	17.3%
		-2 SDS - +2 SDS	67	82.7%
		> +2 SDS	0	0%
BMI SDS		**< -2 SDS**	1	1.2%
		-2 > SDS < +2	75	92.6%
		> +2 SDS	5	6.2%
Waist circumference		**< 75th percentile**	78	96.3%
		75th - 90th percentile	3	3.7%
		>90th percentile	0	0%
SBP (mmHg)		**Normal**	77	95.1%
		Prehypertensive (90th-95th percentile)	4	4.9%
		Hypertensive (> 95th percentile)	0	0%

Preprint

DBP (mmHg)	**Normal**	70	86.1%
	Prehypertensive (90th-95th percentile)	11	13.9%
	Hypertensive (> 95th percentile)	0	0%
Biochemical data			
Mean HbA1c (%)	**Good control (<7%)**	2	2.5%
	Fair control (7-8%)	18	22.2%
	Poor control (>8%)	61	75.3%
Elevated TC (mg/dl)	**Borderline (170-199 mg/dl)**	30	37%
	High (>200 mg/dl)	13	16%
High LDL (>130 mg/dl)		43	53.1%
Low HDL (< 40 mg/dl)		16	19.8%
High TGs (>130 mg/dl)		5	6.2%
Abnormal uACR (mg/g)	**Microalbuminuria (30-300 mg/g)**	25	30.9%
	Macroalbuminuria (>300 mg/g)	1	1.2%
Hypothyroidism (TSH > 4.25 mIU/L)		12	14.8%
Positive Celiac screening		3	3.7%
High NT-proBNP (>125 pg/ml)		73	90.1%

DKA: diabetic ketoacidosis, **BMI**: body mass index, **SBP**: systolic blood pressure**, DBP**: diastolic blood pressure **SD:** standard deviation, **TC:** total cholesterol**, HDL:** High density lipoprotein, **LDL:** Low density lipoprotein, **TGs:** triglycerides, **HbA1c:** glycosylated hemoglobin, **uACR:** urinary albumin creatinine ratio, **NT-proBNP**: N-terminal pro b-type natriuretic peptide

Preprint

Table 2: Cardiomyopathy markers (NT-proBNP and echocardiographic findings) in cases vs non-diabetic controls

		Cases (n=81)	Controls (n=50)	*p* value
Mean +/- SD	**NT-proBNP (pg/ml)**	470.1 ± 362.6	79.6 ± 35.2	**<0.001**
	LV E/E' Average	10.3 ± 4.2	5.9 ± 1.3	**<0.001**
	Tricuspid E'/A'	1.6 ± 0.5	1.7 ± 0.6	0.734
	GLS-LV	13.9 ± 4.3	23.9 ± 1.4	**<0.001**
	GLS-RV	12.4 ± 3.9	18.6 ± 1.1	**<0.001**
Prevalence (%)	**NT-proBNP (> 125 pg/ml)**	73 (90.1%)	0 (0%)	**<0.001**
	LV E/E' (> 8)	41 (50.6%)	1(3.3%)	**<0.001**
	Tricuspid E'/A' (<1)	12 (14.8 %)	0 (0%)	**<0.001**
	GLS-LV (<18)	68 (84%)	0 (0%)	**<0.001**
	GLS-RV (<18)	74 (91.4%)	15(50%)	**<0.001**

NT-proBNP: N-terminal pro b-type natriuretic peptide**, SD:** standard deviation, **E'/A:** Early diastolic tissue velocity/ Atrial diastolic tissue velocity, **E / È:** early mitral inflow velocity / average of the early diastolic tissue velocities of septal and lateral walls, **LV:** left ventricular, **RV:** right ventricle, **GLS:** left ventricular global longitudinal strain

Preprint

Table 3: Correlation between DCM markers (biochemical and echocardiography) and different study parameters

Parameter	Serum NT-proBNP		GLS-RV (RV systolic dysfunction)		GLS-LV (LV systolic dysfunction)		Tricuspid E'/A' (RV diastolic dysfunction)		LV E/E' Average (LV diastolic dysfunction)	
	r	*p* value	r	*p* value	r	*p* value	r	*p* value	r	*p* value
Age (years)	-0.152	0.174	-0.014	0.904	0.173	0.123	-0.041	0.714	-0.118	0.296
Duration of diabetes (years)	0.221	**0.048**	-0.167	0.137	-0.215	**0.05**	0.157	0.161	0.271	**0.015**
Insulin requirements (IU /kg/d)	-0.142	0.208	-0.039	0.730	0.110	0.333	-0.118	0.298	0.077	0.499
Long acting insulin (IU /kg/d)	-0.015	0.892	-0.016	0.888	-0.100	0.375	-0.216	**0.049**	-0.024	0.833
SBP (mmHg)	0.089	0.430	-0.011	0.921	-0.252	**0.023**	0.012	0.912	0.149	0.183
DBP (mmHg)	0.007	0.950	-0.130	0.247	-0.062	0.582	0.089	0.428	0.279	**0.012**
Weight SDS	0.274	**0.013**	0.054	0.632	-0.150	0.262	0.025	0.827	-0.111	0.326
Height SDS	0.066	0.556	0.011	0.922	-0.150	0.181	0.117	0.299	-0.038	0.737
BMI SDS	0.167	0.137	0.058	0.608	-0.171	0.127	-0.030	0.792	-0.116	0.303
Waist circumference (cm)	0.125	0.266	0.009	0.936	-0.043	0.705	-0.150	0.181	-0.089	0.427
Stage of puberty	-0.155	0.168	0.050	0.656	0.148	0.187	0.042	0.711	-0.119	0.291
Frequency of DKA	-0.079	0.556	0.115	0.392	-0.043	0.751	-0.150	0.262	0.343	**0.008**
Serum creatinine (mg/dl)	0.066	0.556	0.040	0.722	-0.030	0.788	-0.252	**0.023**	0.061	0.586
NT-proBNP (pg/ml)			0.157	0.161	-0.796	**<0.001**	-0.027	0.808	-0.109	0.332
Fasting blood glucose (mg/dl)	-0.026	0.818	-0.200	0.074	0.001	0.996	-0.143	0.201	0.275	**0.013**
HbA1c (mg/dl)	-0.095	0.398	-0.158	0.159	0.010	0.927	-0.102	0.363	0.241	**0.030**
TC (mg/dl)	0.144	0.199	-0.149	0.183	-0.171	0.128	-0.191	0.087	-0.252	**0.023**
LDL (mg/dl)	0.170	0.128	0.058	0.609	-0.179	0.110	-0.252	**0.023**	0.119	0.291
HDL (mg/dl)	-0.118	0.292	-0.055	0.626	-0.114	0.311	0.118	0.295	0.014	0.904
TGs (mg/dl)	-0.022	0.844	-0.025	0.826	-0.271	**0.015**	-0.228	**0.041**	0.108	0.338
uACR (mg/g)	-0.063	0.579	-0.220	**0.049**	-0.020	0.856	-0.029	0.796	0.176	0.116

DKA: diabetic ketoacidosis, **BMI**: body mass index, **SBP**: systolic blood pressure**, DBP**: diastolic blood pressure **SD:** standard deviation, **TC:** total cholesterol**, HDL:** High density lipoprotein, **LDL:** Low density lipoprotein, **TGs:** triglycerides, **HbA1c:** glycosylated hemoglobin, **uACR:** urinary albumin creatinine ratio, **NT-pro BNP**: N-terminal pro b-type natriuretic peptide, **E'/A:** Early diastolic tissue velocity/ Atrial diastolic tissue velocity, **E / È:** early mitral inflow velocity / average of the early diastolic tissue velocities of septal and lateral walls, **LV:** left ventricular, **RV:** right ventricle, **GLS:** left ventricular global longitudinal strain

Preprint

Preprint

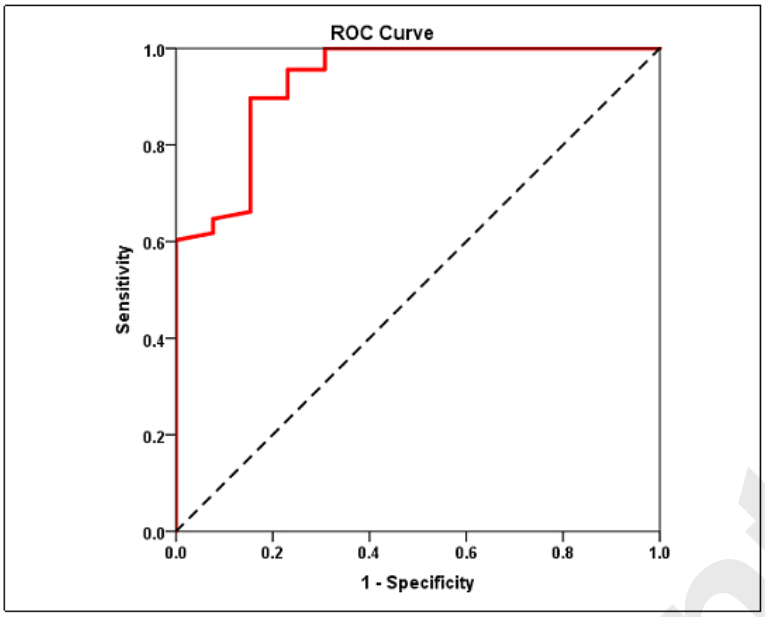
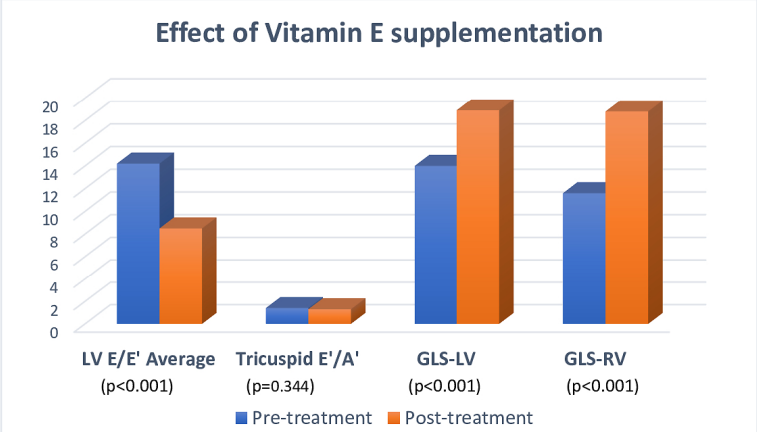


Figure 1: ROC curve analysis to explore the discriminate ability of NT-pro-BNP in differentiating STE LV systolic dysfunction

AUC	*95% CI*	*Cut-off*	*Sensitivity*	*Specificity*
0.932	*0.856-1.000*	*≥ 195*	*89.7%*	*84.6%*

***AUC**= area under the curve, **CI**= confidence interval*

Preprint


Effect of Vitamin E supplementation
20
18
16
14
12
10
8
6
4
2
0
LV E/E' Average
(p<0.001)
Tricuspid E'/A'
(p=0.344)
GLS-LV
(p<0.001)
GLS-RV
(p<0.001)
Pre-treatment
Post-treatment

Preprint