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# Role of epicardial fat thickness and irisin levels in early prediction of cardiac dysfunction in children and adolescents with type 1 diabetes mellitus

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## ABSTRACT

**Introduction:** to assess the role of epicardial fat thickness and irisin in early prediction of cardiac dysfunction in children and adolescents with type 1 diabetes mellitus and correlate them with echocardiographic parameters and lipid profile.

**Material and methods:** Sixty-three type 1 diabetic children and adolescents were recruited from the Pediatric Diabetic Clinic, National Research Centre. Thirty-four healthy children, matched for age and sex, served as controls. All patients were insulin dependent with at least 3-year duration of the disease since diagnosis. Venous blood was withdrawn under complete aseptic precautions from fasting subjects; sera were collected for evaluation of glycated haemoglobin ($HbA_{1C}$), lipid profile and irisin levels. Two-dimensional echocardiography was performed for measurement of interventricular septal thickness in diastole, left atrial diameter (LAD), aortic root diameter, mitral E and A wave, left ventricular internal dimension in diastole, percent fractional shortening (FS%), percent ejection fraction, left ventricular mass, and epicardial fat thickness. Patients were further divided into two groups according to their glycaemic control (< 7.00, ≥ 7.0) for comparison of echocardiographic parameters and irisin.

**Results:** Echocardiographic study revealed a statistically significant increase in LAD, FS%, and epicardial fat thickness in patients compared to controls ($p$ = 0.000, 0.014, and 0.000 respectively). Triglyceride and irisin levels were significantly increased in patients compared to controls ($p$ = 0.012, 0.015 respectively). Epicardial fat thickness positively correlated with left atrial diameter ($p$ = 0.009) and left ventricular mass ($p$ = 0.000). Irisin was positively correlated with E/A ratio ($p$ = 0.05).

**Conclusions:** The findings of the present study probably indicate the beginning of a state of metabolically induced diastolic dysfunction. Echocardiography should be performed in type 1 diabetic patients on a regular basis for early detection of subclinical cardiac dysfunction.

KEY WORDS:

**epicardial fat thickness, type 1 diabetes mellitus, cardiac dysfunction, children.**

## INTRODUCTION

The incidence of diabetes mellitus (DM) has gradually increased, becoming a serious public health threat. Cardiovascular complications in type 1 diabetes (T1DM) is the leading cause of death in those patients [1]. Specific risk factors that predict cardiac abnormalities in such patients are yet not fully elucidated. Diabetic cardiomyopathy, defined as the changes that occur in cardiac functions and structure in the absence of hypertension,

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ischemic cardiac disease or other heart pathologies, can be subclinical or apparent. At first, there is diastolic dysfunction, followed by subclinical systolic dysfunction with preserved ejection fraction, which progresses with time to heart failure with diminished ejection fraction. Echocardiography is an important tool which provides an easy, convenient and accurate tool in assessment of systolic and diastolic functions in children and adolescents with type 1 diabetes mellitus [2].

Accumulation of visceral fat is an important risk factor for insulin resistance, which can reduce insulin sensitivity, increase the expression and secretion of pro-inflammatory cytokines in adipose tissue and promote the development of cardiovascular diseases [3]. Epicardial fat tissue (EFT) is a type of visceral adipose tissue which surrounds the myocardium and pericardium and is considered as the visceral fat store in the body. Measurements of EFT in previous studies have suggested that it is a substitute for visceral fat. EFT thickness measured by echocardiography has recently become a simple practical tool for cardiovascular risk stratification [4].

Irisin is a newly discovered adipo-myokine that has a role in energy and thermogenesis homeostasis. It is a 112 amino acid protein of 12 kDa molecular weight, and is a product of fibronectin type III domain 5(FNDC5) cleavage [5]. Irisin converts white adipose tissue into brown adipose tissue, and is believed to improve glucose metabolism and reverse visceral obesity[6]. Irisin has been proven to play a role in cardiomyoblast metabolism and blood pressure (BP) control [7]. Previous studies have claimed the role of irisin in obesity, insulin resistance and type 2 diabetes [8]. However, its role in type 1 diabetic youth is yet to be clarified.

Low HDL cholesterol is the most frequent dyslipidaemic disorder in poorly controlled subjects with T1DM [9], and some qualitative alterations have been reported in HDL cholesterol, especially in subjects with long-term diabetes [10]. It remains unknown how EFT affects or is affected by these alterations in HDL and how it contributes to the emergence of atherosclerotic disease in T1DM.

The aim of the present work is to assess the role of epicardial fat thickness and irisin hormone in early prediction of cardiac dysfunction in children and adolescents with type 1 diabetes mellitus and correlate them with other studied echocardiographic parameters and lipid profile.

## MATERIAL AND METHODS

This was a prospective cross-sectional study involving 63 T1DM children and adolescents (28 males and 35 females) with the age range 6–18 years. Thirty-four children, matched for age and sex, served as a control group and were recruited from the Pediatric Diabetic Clinic, Centre of Excellence, National Research Centre during the period 2019 to 2021.

The study protocol was approved by the Human Ethics Committee of the National Research Centre as a part of project No. 19-223, and written informed consent was obtained from all parents/legal guardians of children, after providing full knowledge about the aims of the study. Funding source: National Research Centre.

All participants were subjected to full history taking and clinical evaluation to fulfil the required data: insulin therapy, dose in units/kg and type. History suggestive of any acute or chronic cardiac involvement was requested. Our cases were diagnosed as T1DM according to the definition of the World Health Organization, and are all currently insulin dependent with at least 3-year duration of the disease since diagnosis. Children with secondary DM or who suffered from any acute or chronic illnesses related to cardiac condition were excluded from the study. Patients were further divided into two groups according to their glycaemic control to compare studied echocardiographic parameters, epicardial fat thickness and irisin levels between the two groups. Group 1 patients were considered to have good glycaemic control (< 7.00), whereas group 2 had a glycated haemoglobin ($HbA_{1c}$) level of ≥ 7.00. An $HbA_{1c}$ level of 7.00 or below in diabetic patients was shown to be accompanied by a reduction in microvascular and macrovascular complications [11].

Blood pressure was measured according to American Heart Association guidelines: three times for patients and controls after a five-min rest in a sitting position with the use of a mercury sphygmomanometer. The mean value of the second and third measurement was calculated. Systolic blood pressure (SBP) was defined as the onset of the Korotkoff sound (K1), and diastolic blood pressure (DBP) was defined as the fifth Korotkoff sound (K5). Anthropometric indices included the following: body weight measured to the nearest 0.1 kg with a balance scale and height measured to the nearest 0.1 cm. Body mass index was calculated as weight divided by height squared (kg/m$^2$). Waist circumference (WC) was measured at the level midway between the lowest rib margin and the iliac crest. Hip circumference (HIP C) was measured at the widest level over the greater trochanters in a standing position by the same examiner, then waist to hip ratio (WHR) and waist to height ratio (WHtR) were calculated [12].

### LABORATORY PARAMETERS

Venous blood was withdrawn under complete aseptic precautions from fasting subjects (12–14 hours). Samples were labelled and left to clot at room temperature for 15 minutes then centrifuged, sera were collected and aliquoted for evaluation of the following parameters: pertinent laboratory investigations were performed for all patients including $HbA_{1c}$, levels and lipid profile (cholesterol, triglyceride, HDL and LDL, using an Olympus AU 400 autoanalyser supplied from Olympus Life and Material Sci-

**TABLE 1.** Clinical characteristics of studied diabetic patients ($N = 63$) and control group ($N = 34$)

| Variable | Diabetic patients (mean ± SD) | Controls (mean ± SD) | Sig. (2-tailed) |
|---|---|---|---|
| Age [years] | 12.82 ±3.24 | 11.65 ±3.54 | 0.077 |
| Sex, male/female | 28/35 | 16/18 | |
| Duration of diabetes [years] | 5.35 ±3.75 | – | |
| BMI | 21.15 ±4.10 | 18.72 ±4.10 | 0.003 |
| Systolic BP [mm Hg] | 109.76 ±11.32 | 104.58 ±9.20 | 0.029 |
| Diastolic BP [mm Hg] | 71.37 ±7.30 | 71.25 ±5.57 | 0.754 |
| WC [cm] | 73 ±11.10 | 75.87 ±15.64 | 0.517 |
| HIPC [cm] | 85.08 ±13.05 | 62.79 ±13.05 | 0.000 |
| WHR | 0.86 ±0.057 | 0.82 ±0.070 | 0.003 |
| Insulin [IU/ kg/day] | 1.94 ±1.7 | – | |

*WC – waist circumference, HIPC – hip circumference, WHR – waist to hip ratio.*

ence, Europe GmbH, Wendenstraße, Hamburg, Germany), serum levels of irisin were quantitatively estimated employing the enzyme immunosorbent assay technique using an ELAbscience kit, USA (Cat. No E-EL-H6120).

### ECHOCARDIOGRAPHY EXAMINATION

Echocardiography was performed using Vivid 3 Pro GE Vingmed (Norway) by standard technique using a 3-MHz transducer. Each subject underwent a transthoracic 2-dimensional M-mode echocardiography with the subject in the supine and left lateral decubitus positions. Conventional measurements were recorded: interventricular septal thickness in diastole (IVSd ), left atrial diameter (LAD), aortic root diameter, mitral E and A wave measurements as well as E/A calculation, left ventricular internal dimension in diastole (LVIDd), left ventricular posterior wall diameter in diastole (LVPWd), percent fractional shortening (%FS), and percent ejection fraction (%EF). Left ventricular mass (LV mass) was estimated using the formula of Devereux *et al.* [13], as well as epicardial fat thickness, which was measured on the free wall of the right ventricle perpendicular to the wall, from the parasternal long axis view with optimal cursor view orientation at end diastole. Epicardial fat tissue appeared as an echo free space [14].

### STATISTICAL ANALYSIS

Analysis of our results was carried out using the standard computer program SPSS for Windows, release 17.0 (SPSS Inc., USA). All numerical variables were expressed mean ± standard deviation (SD). The intergroup comparisons were performed using an independent-sample t test and a one-way analysis of variance and chi-square tests for categorical variables. Pearson's and Spearman's correlation tests ($r$ = correlation coefficient) were used for the correlation of normal and nonparametric variables, respectively.

Multiple linear regression analysis was used to evaluate the independent predictor in those subjects. For all tests, $p \leq 0.05$ was considered significant and $p < 0.01$ was considered highly significant.

## RESULTS

A total of 97 participants were registered in the present study (63 diabetic patients and 34 age- and sex-matched controls). The mean age of patients was 12.82 ±3.24 years, 28 (44.4%) were boys, and 35 (55.6%) were girls. The mean insulin/kg dose was 1.94 ±1.7 IU, and the mean disease duration was 5.35 ±3.75 years. No patients were hypertensive or had associated autoimmune or celiac diseases. BMI of our cases was within normal the range for age and sex.

The clinical findings of studied patients and the control group are presented in Table 1.

Table 2 shows the results of 2D echocardiographic study for patients and healthy controls. The findings reveal statistically significant differences in LAD, LA/AO, FS%, and epicardial fat thickness in patients compared to healthy controls ($p$ = 0.000, 0.000, 0.014, and 0.00 respectively).

Table 3 shows the laboratory results of diabetic patients compared to the control group. There are statistically significant differences between our cases and controls as regards TG, $HbA_{1c}$ and irisin ($p$-value: 0.012, 0.000 and 0.015) respectively.

Table 4 presents a comparison of mean irisin levels and studied echocardiographic parameters in the two studied groups according to $HbA_{1c}$ level (< 7.00, ≥ 7.00). When our patients were divided into two groups according to $HbA_{1c}$ level there was no significant difference in all studied parameters.

Correlations between different clinical, echo and laboratory parameters were studied. Correlations of epicardial fat thickness with echo parameters showed significant positive correlations with IVSd ($r$ = 0.335, $p$ = 0.008), aortic root ($r$ = 0.326, $p$ = 0.01), left atrial diameter ($r$ = 0.331,

**TABLE 2.** Echocardiographic characteristics of studied patients and healthy controls

| Echo characteristics | T1DM (1)/ Controls (2) | Mean | Std. deviation | Sig. (2-tailed) |
|---|---|---|---|---|
| IVSd [cm] | 1 | 0.6790 | 0.16453 | 0.235 |
| | 2 | 0.7167 | 0.10279 | |
| LAD [cm] | 1 | 2.6037 | 0.39784 | 0.000 |
| | 2 | 2.1006 | 0.34632 | |
| LA/Ao ratio | 1 | 1.2321 | 0.19276 | 0.000 |
| | 2 | 1.6638 | 0.28170 | |
| E/A ratio | 1 | 1.6944 | 0.3455 | 0.305 |
| | 2 | 1.6219 | 0.27538 | |
| LVIDd [cm] | 1 | 4.1310 | 0.57356 | 0.344 |
| | 2 | 4.0164 | 0.52601 | |
| LVPWd [cm] | 1 | 0.6150 | 0.17051 | 0.055 |
| | 2 | 0.7124 | 0.12240 | |
| FS% | 1 | 39.2185 | 8.35481 | 0.014 |
| | 2 | 35.4030 | 3.43306 | |
| EF% Teich | 1 | 69.22 | 8.633 | 0.344 |
| | 2 | 66.32 | 3.420 | |
| LV mass [g] | 1 | 78.8323 | 30.53053 | 0.792 |
| | 2 | 77.2152 | 23.62214 | |
| Epicardial fat thickness [mm] | 1 | 7.0180 | 1.85737 | 0.000 |
| | 2 | 2.1692 | 0.58933 | |

*IVSd – interventricular septal thickness in diastole, LAD – left atrial diameter, LVIDd – left ventricular internal dimension in diastole, LVPWd – left ventricular posterior wall diameter in diastole, FS% – percent fractional shortening, EF% – percent ejection fraction, T1DM – type 1 diabetes mellitus patients.*

**TABLE 3.** Laboratory parameters of studied patients and healthy controls

| Variable | Diabetic patients (1)/ healthy children (2) | Mean | ± SD | *P*-value |
|---|---|---|---|---|
| Cholesterol [mg/dl] | 1 | 163.96 | 22.633 | 0.559 |
| | 2 | 161.00 | 25.98 | |
| TG [mg/dl] | 1 | 82.53 | 25.11 | 0.012 |
| | 2 | 71.4250 | 12.54 | |
| HDL [mg/dl] | 1 | 43.62 | 16.98 | 0.606 |
| | 2 | 45.18 | 9.72 | |
| LDL [mg/dl] | 1 | 63.09 | 6.99 | 0.166 |
| | 2 | 60.15 | 13.10 | |
| $HbA_{1c}$ | 1 | 7.77 | 1.51 | 0.000 |
| | 2 | 4.77 | .45 | |
| Irisin [ng/ml] | 1 | 4.26 | 2.39 | 0.015 |
| | 2 | 3.16 | 1.63 | |

*TG – triglycerides, HDL – high density lipoprotein, LDL – low density lipoprotein, $HbA_{1c}$ – glycated haemoglobin.*

$p = 0.009$) (Figure 1), left ventricular mass ($r = 0.498$, $p = 0.000$) (Figure 2), left ventricular internal dimension in diastole ($r = 0.345$, $p = 0.006$) and left ventricular posterior wall thickness ($r = 0.259$, $p = 0.044$). It was also significantly correlated with body mass index ($r = 0.334$, $p = 0.009$), % body fat ($r = 0.306$, $p = 0.016$), triglycerides ($r = 0.323$, $p = 0.021$) and $HbA_{1c}$ ($r = 0.361$, $p = 0.003$), but not correlated with irisin. Evaluation of different risk factors by linear regression analysis was used to explore the independent determinants of epicardial fat thickness. Different predictors were $HbA_{1c}$, LV mass, and TG. ANOVA revealed that the strongest association existed between epicardial fat

**TABLE 4.** Comparison of mean irisin levels and studied echocardiographic parameters in the two studied groups according to $HbA_{1c}$ level (< 7.00, ≥ 7.00)

| Variable | $HbA_{1c}$ level | *N* | Mean | Std. deviation | *P*-value |
|---|---|---|---|---|---|
| Irisin [ng/ml] | ≥ 7.00 | 35 | 4.3171 | 2.49535 | 0.782 |
| | < 7.00 | 12 | 4.0917 | 2.15215 | |
| IVSd | ≥ 7.00 | 46 | 0.6737 | 0.17125 | 0.719 |
| | < 7.00 | 17 | 0.6906 | 0.14372 | |
| Aortic root | ≥ 7.00 | 46 | 2.1426 | 0.34562 | 0.975 |
| | < 7.00 | 17 | 2.1394 | 0.39825 | |
| LAD | ≥ 7.00 | 46 | 2.6346 | 0.41706 | 0.268 |
| | < 7.00 | 17 | 2.5094 | 0.32275 | |
| LA/AO | ≥ 7.00 | 46 | 1.2470 | 0.19663 | 0.381 |
| | < 7.00 | 17 | 1.1988 | 0.17885 | |
| LVIDd | ≥ 7.00 | 46 | 4.1117 | 0.60663 | 0.850 |
| | < 7.00 | 16 | 4.1438 | 0.49138 | |
| FS% | ≥ 7.00 | 46 | 39.3148 | 7.23012 | 0.973 |
| | < 7.00 | 17 | 39.3965 | 11.06845 | |
| EF% Teich | ≥ 7.00 | 46 | 70.08 | 8.598 | 0.288 |
| | < 7.00 | 17 | 67.45 | 8.764 | |
| Left ventricular mass | ≥ 7.00 | 46 | 79.0624 | 33.46120 | 0.735 |
| | < 7.00 | 17 | 76.0213 | 20.97052 | |
| Epicardial fat thickness | ≥ 7.00 | 45 | 7.1800 | 2.03834 | 0.231 |
| | < 7.00 | 17 | 6.5471 | 1.11081 | |

*IVSd – interventricular septal thickness in diastole, LAD – left atrial diameter, LVIDd – left ventricular internal dimension in diastole, FS – fractional shortening, EF – ejection fraction.*

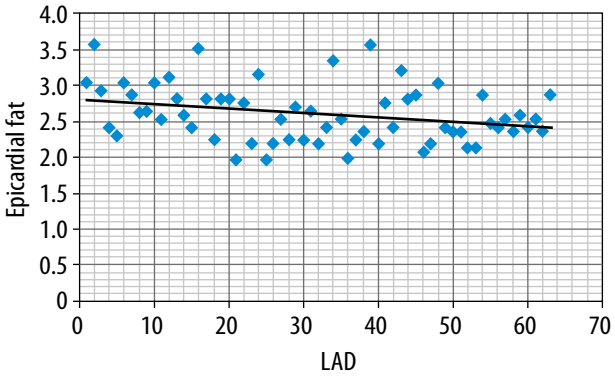


**FIGURE 1.** Relation between epicardial fat thickness and left atrial diameter (LAD) in diabetic children

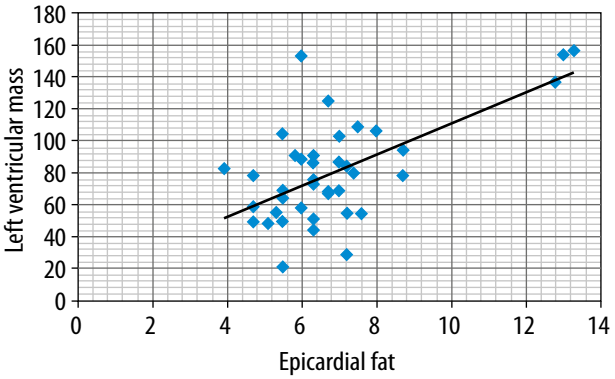


**FIGURE 2.** Relation between epicardial fat thickness and left ventricular mass in diabetic children

thickness and LV mass ($p = 0.000$). As regards the hormone irisin, it was negatively correlated with interventricular septum thickness ($r = -0.283$, $p = 0.046$) and left ventricular internal dimension ($r = -0.288$, $p = 0.042$), whereas there was a positive correlation with E/A ratio ($r = 0.284$, $p = 0.05$). Irisin was not correlated with other echocardiographic parameters, lipid profile or $HbA_{1c}$ (data not shown).

## DISCUSSION

Cardiac dysfunction is a common cause of morbidity and mortality in patients with type 1 diabetes mellitus. There is an urgent need for an available easy tool for early detection of subclinical dysfunction as early as possible to minimize adverse events. In the present study, children and adolescents with type 1 diabetes mellitus underwent conventional echocardiography as well as measurement of a novel hormone, a myokine, namely, irisin. Echocardiography revealed a significant increase in epicardial fat thickness, left atrial diameter and % FS in patients compared to healthy children (Table 2). Previous studies have shown an increase in epicardial fat in children with type 1 diabetes mellitus with no obesity or symptoms of cardiac affection, similar to our patients [14, 15].

As epicardial fat has been shown to be a form of visceral adipose tissue, these authors suggested it to be a metabolic and cardiovascular risk factor. Left atrial diameter was significantly increased in accordance with Abd-El Aziz *et al.* and Flachskampf *et al.* [16, 17]. They mentioned that an enlarged left atrium is a sign of increased left atrial pressure which has developed over time. They also stated that this enlargement in the left atrium may persist for some time after normalization of left atrial pressures. Left ventricular thickness was normal in our studied patients in accordance with previous studies [18, 19]. On the other hand, Bjornstad *et al.* [20] reported that there was increased left ventricular thickness in their children with type 1 diabetes and explained that this could happen to maintain a normal left ventricular systolic function. As regards E/A ratio, studies have shown controversial results. Whereas in the present study there was no difference between patients and healthy children, other studies have found a decreased ratio denoting early diastolic dysfunction. In agreement with our results, studies by Labombarda *et al*. and Bradley *et al*. [18, 19] reported that patients with diabetes had a normal E/A ratio; on the other hand, Yoldaş *et al*. and Altun *et al*. [21, 22] found the E/A ratio to be decreased. Previous studies attributed this controversy to several factors such as duration of disease, glycaemic control, demographic characteristics related to the patient and different imaging technique. In a previous study, diastolic dysfunction denoting early cardiomyopathy was detected in 7.5% of their studied patients by conventional echocardiography [23]. Percent fractional shortening was significantly increased in our patients, which was in concordance with a study by Gotzsche *et al.* [24]. They explained that this phenomenon in early diabetic patients might be due to a sympathetic/parasympathetic imbalance; moreover, these patients might have a state of metabolically induced cardiomyopathy with reduced left ventricular cavity size associated with increased atrial ejection. Contrary to our results, in a study by Abd-El Aziz *et al.* [16], they found significantly lower % FS in children and adolescents with type 1 diabetes mellitus compared to healthy controls, yet it was within the normal range. They attributed this finding to early impairment of systolic function in their studied population.

In the present work, total cholesterol, triglycerides, HDL, LDL, irisin hormone and $HbA_{1c}$, as an index of glycaemic control in patients with diabetes, were measured and compared to healthy children. Triglyceride and irisin levels were significantly increased in patients versus control children. There was a highly significant difference in HbA1c in patients compared to healthy children (Table 3). Packer in 2018 [25] explained that the increase in lipid profile could be attributed to the increase in epicardial fat tissue which under certain conditions secretes excess fatty acids, leading to abnormal lipid indexes such as total cholesterol and triglycerides. Several research workers have studied irisin in type 1 diabetes and found it to be increased in comparison to controls [26]. Aydin *et al.* [27] explained that since irisin is present in the pancreas, its destruction in diabetes could lead to an increase in irisin levels. On the other hand, in another study by Akyuz *et al.*[28] on adult patients with diabetes on insulin treatment, irisin levels were found to be lower than in controls. This discrepancy could be due to the age difference and duration of illness.

We further divided diabetic children into two groups according to glycaemic control (< 7, and ≥ 7). The mean levels of epicardial fat thickness, irisin and echocardiographic parameters did not differ between groups. A possible explanation is the fair to good glycaemic control of our patients, who had a mean glycaemic control of 7.77. According to the American Diabetes Association (ADA), the optimal level of $HbA_{1c}$ is < 8 for ages 6 to 12 years and < 7.5 for those above 12 years of age due to the risk of hypoglycaemia in these patients [29].

We studied the different correlations between studied parameters, focusing on epicardial fat thickness and irisin. Epicardial fat thickness positively correlated with echocardiological parameters, namely, left atrial diameter (Figure 1), LV mass (Figure 2) and LVPWd. It was also correlated with BMI, % body fat, triglycerides and HbA1c, yet was not correlated with irisin, E/A ratio or other studied lipid profile parameters. Çetin *et al.* [30] showed that increased epicardial fat was associated with enlargement of atrial dimension and increase in left ventricular mass, in accordance with our results. Moreover, Iacobellis *et al.* [31] studied the relation between epicardial fat and LV mass and found a strong association. They deduced that this relationship could be related to the fact that both epicardial fat and left ventricular mass are cardiac risk factors, and further explained that this increased epicardial fat which represents visceral fat could directly increase the LV output and stroke volume in order to perfuse the increased ventricular mass. Irisin was negatively correlated with the echo parameters IVSd and LVIDd. It had a borderline positive correlation with E/A ratio ($p = 0.05$), and no correlation with lipid profile or $HbA_{1c}$. In agreement with our results, Tang *et al.* [32] did not find any correlation between irisin and lipid profile. Furthermore, Faienza *el al.* [33] noted that high irisin levels in patients with diabetes were correlated with better glycaemic control, in concordance with our results.

A limitation of the present study was the relatively small number of children involved, who were recruited from one centre.

## CONCLUSIONS

Our patients had fair to good glycaemic control as well as relatively short duration of type 1 diabetes. Yet, they showed an increase in epicardial fat thickness, left atrial diameter, left ventricular mass and % fractional shortening

by echocardiography as well as increase in triglycerides and irisin levels compared to healthy children. These findings probably indicate the beginning of a state of metabolically induced left ventricular diastolic dysfunction. Moreover, irisin hormone was negatively correlated with left ventricular end diastolic dimension and positively correlated with E/A ratio. We recommend that echocardiography should be performed for patients with type1 diabetes on a regular basis for early detection of subclinical cardiac dysfunction, thus reducing the risk of morbidity and mortality in this patient cohort. Future studies are warranted to elucidate the exact role of irisin hormone in type 1 diabetics.

## DISCLOSURE

The authors declare no conflict of interest.

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