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Assessment of Interleukin 27 Serum Levels and Echocardiographic Parameters in Children and Adolescents with Type 1 Diabetes Mellitus

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ABSTRACT

Background: New treatment methods for cardiovascular and autoimmune illnesses take advantage of (IL-27) pro- and anti-inflammatory properties. **Objective**: To assess the level of IL-27 level and echocardiographic parameters in children, and adolescents with type 1 diabetes mellitus (T1DM).

Patients and Methods: at Department of Pediatrics, Diabetes Outpatient and Echocardiography Cardiology Unit, Zagazig University Hospitals, we conducted this case-control study on 30 children diagnosed with T1DM and 30 healthy age- and sex-matched subjects who were selected as non-diabetic group (controls). Serum lipid and IL-27 measurements in addition to echocardiography were done.

Results: There was significant higher value of following echocardiography measures: LVIDs, LVIDd, LVId, LVIsd, PWD S, PWD D, RWT, LVMI, LVM both of bad and good control diabetic children compared to healthy control. While there was no significant difference regarding EF and FS between studied groups. There was significant higher value of serum interleukin 27 of bad control diabetic children compared to both; good control diabetic children and healthy children. But there was no significant difference, of good control diabetes children and healthy control children regarding serum interleukin 27. There was significant positive relation between serum interleukin 27 and disease duration of bad control type1 diabetic children.

Conclusion: T1DM is connected with rise of IL-27 levels and lipid profile. This link is particularly evident in poorly managed patients demonstrating a relevant involvement of IL- 27 and dyslipidemia on the etiology of the condition.

Keywords: Cardiovascular, Interleukin 27, Type 1 Diabetes Mellitus

INTRODUCTION

High-risk individuals, such as those with DM, should be given extra attention. In those with diabetes, CVD is the primary cause of death and disability[(1)]. Atherosclerosis is twice to four times more likely to occur in people with diabetes. Having type 1 diabetes is a significant risk factor for CVD. T1DM should be given more attention because it affects younger people and lasts longer than other forms of diabetes[(2)].

Patients with diabetes have accelerated atherosclerosis and early CVD consequences for a variety of reasons that are as yet unresolved [(3)]. Female diabetics are more likely to develop coronary heart disease than male diabetics, especially those with (T1DM)[(4)]. There is a clear link between high HbA1c levels and an elevated risk of heart failure and cardiovascular disease death. In addition, cholesterol (HDL-C and LDL-C) are powerful predictors of cardiovascular disease in non-diabetic children and adults as well as in those with type 1 diabetes [(5)].

As a result, blood pressure regulation is helpful in reducing cardiovascular morbidity and death in diabetics [(6)]. A cost-effective and time-saving procedure, echocardiography delivers accurate and repeatable diagnostic and prognostic information in patients with diabetes mellitus [(7)]. Diabetes patients can be thoroughly studied with the use of two-dimensional and speckle-track echocardiography [(8)]. However, little is known regarding the progression of early cardiac structural and functional problems in children with T1DM, as prior echocardiographic studies have demonstrated varying changes in left ventricular shape, mass, and function [(9)].

Pro-inflammatory and anti-inflammatory effects can be achieved by interlukin-27 (IL-27), which is now being used in novel treatment approaches for cardiovascular and autoimmune disorders[(10)]. T1DM development and immunological balance maintenance are both likely to be influenced by the ability to express IL-27 [(11)].

It was the goal of this study to assess the level of IL-27 and echocardiographic parameters in children, and adolescents with (T1DM).

SUBJECTS AND METHODS

At Department of Pediatrics, Diabetes Outpatient and Echocardiography Cardiology Unit of Pediatrics Department, Faculty of Medicine at Zagazig University Pediatric Hospital, sixty children were included in the study, 30 children were diagnosed with T1DM, which was confirmed according to the criteria of American Diabetes Association (ADA) guideline, and 30 healthy age- and sex-matched subjects who were selected as non-diabetic group (controls).

Ethical consent:

Research Ethics Council at Zagazig University approved the study (ZU-IRB#6891) as long as all parents of participants provided

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informed consent forms. Ethics guidelines for human experimentation by the World Medical Association's Helsinki Declaration were adhered to.

Inclusion criteria: Children aged from 8 to 16 years, both gender, patients diagnosed with having T1DM according to the criteria of American Diabetes Association, all included cases were treated with human insulin therapy and HbA1c < 10%.

Exclusion criteria: Patients with known cardiovascular problems, metabolic illnesses other than diabetes, and those who refused to give their consent were excluded from the trial.

The studied population was divided into:

Case group: A case-control study was conducted on 30 children diagnosed with T1DM. All diabetic patients were divided into bad and good glycemic control groups. According to the American Diabetes Association (ADA) published the target age-specific HbA1c as follow: <6 years, 7.5%-8.5%; from 6 to 12 years, ≤8%; from 13 to18 years, ≤7.5%. Those patients with HbA1c above the recommended values for age by the ADA were considered as poor glycemic control group.

Control group: included 30 healthy children matched for age and sex. Those patients were void of any history of diabetes or cardiovascular disease.

This is what all of the participants in this research had to go through:

- Full history taking including: Age, sex, education status, age at onset of T1D, and duration of disease, family history; daily activity.
- Thorough clinical examination: with special emphasis on vital data, and all body systems examination, to assess the blood pressure and anthropometric measurements.
- Echocardiography investigation: Doppler scans and 2-dimensional echocardiograms were both carried out and studied in detail.
- Biochemical assessment including CBC, RBS, glycosylated hemoglobin, fasting lipid profile and serum IL-27 Measurements.

Serum IL-27 Measurements: Using an (ELISA) to measure the concentration of (IL-27) in samples.

Echocardiography measurement: All children underwent transthoracic echocardiographic examination using GE Vivid 7 equipment with a 7s MHz (Norway) transducer following parameters were measured:

A) Left ventricular dimensions (LVD): measured from the derived M-mode echocardiography in the parasternal long axis view to assess the following parameters: (1) Interventricular septum thickness at end-diastole [IVSd], end systole [IVSs]. (2) Left ventricular internal diameter at end-diastole [LVIDd], end systole [LVIDs]. (3) Left ventricular posterior wall at end-diastole [LVPWd], end systole [LVPWs]

B) Left ventricular systolic functions were determined as well through estimation of: (1) Ejection fraction (EF%). This method derived from a 2D image is recommended to assess the LV EF. (2) Fractional shortening (FS%).

C) Left ventricular mass (LVM gm).

D) Left ventricular mass index (LVMI gm/m^2): (1) Reference range of female and male 43-95. (2) Mildly abnormal 49-115. (3) Measurements were determined with standard techniques in accordance with the recommendations of the American Society Echocardiography (ASE).

E) Relative wall thickness (RWT): Defined as the ratio of LV wall thickness to LVID, and Reference range of RWT is 0.32 to 0.42.

Statistical analysis

In order to analyze the data acquired, Statistical Package for the Social Sciences (SPSS) version 20 was used. The quantitative data were presented in the form of the mean, median, standard deviation, and range. The information was also presented using qualitative statistics such as frequency and percentage. The student's t test was used to assess the data while dealing with quantitative independent variables. Chi-Square was used to assess qualitatively independent data. The significance of a P value of 0.05 or less was determined.

RESULTS

Table 1 shows that there was not statistically significant difference between type 1 diabetes children and healthy control regarding to sex, age, education and daily activity. More than one half (53.3%) of diabetic cases have positive family history with significant difference from control group.

Table (1): Characteristics of the studied groups

	Type I diabetes children n.30	healthy control n.30	Test of sig	p
Sex n. (%) Males Females	 17 (56.7%) 13 (43.3%)	 15 (50%) 15 (50%)	χ^2 0.27	0.60
Age per year Mean± SD (range)	10.7±2.7 (6-15)	10.2±1.68 (7-14)	t. 0.85	0.39
Family history (%) Positive Negative	 16 (53.3%) 14 (46.3%)	 0 (0.0%) 30 (100%)	χ^2 21.8	0.0001
Education Yes	30 (100%)	30 (100%)	-	-
Daily activity Yes	30 (100%)	3 0(100%)	-	-

Age at disease onset ranged from 2 – 12.4 years old. Duration of disease ranged from 1-10 years. Almost all type1 diabetic children were treated with long acting insulin. 46.7% of type1 diabetic children had good control **(Table 2).**

Table (2): Clinical characters of type 1 diabetic children (n. 30)

Variables	
Age at disease onset Mean ± SD Median (range)	 7.3±3.14 7.9 (2-12.4)
Disease duration / years Mean ± SD Median (range)	 3.5±2.5 3 (1-10)
Insulin Types	
Long acting insulin • Lantus • Trisiba • Dose	 29 (96.7%) 1 (3.3%) 15 (7-30)
Rapid acting l insulin • Actrapid • Apidra • homolog • Novorapid • Dose (unit)	 3 (10%) 16 (53.3%) 1 (3.3%) 6 (20%) 19 (10-72)
Frequency/day • One • Three	 1 (3.3%) 3 (96.7%)
Control of disease • Good control • Bad control	 14 (46.7%) 16 (53.3%)

There was significant lower value of weight, BMI of type1 diabetic children compared to healthy control children. There was significant higher value of DBP of type 1 diabetic children compared to healthy control children **(Table 3).**

Table (3): Anthropometric, systolic and diastolic blood pressure of studied groups

	Good control diabetes children (n.14)	Bad control diabetes children (n.16)	Healthy control (n.30)	F	Post hoc test
Weight(kg) Mean ± SD Median (range)	 37.6±9.1 39.5 (18- 49)	 32.3±11.7 28.5 (17- 51)	 41±10.1 38.5 (24-63)	 3.7 P=0.029	(0.16)* (0.31)** (0.008)***
Height (m) Mean ± SD Median (range)	 1.47±0.15 1.52 (1.1- 1.63)	 1.45±0.17 1.48 (1.1-1.63)	 1.39 ±0.12 1.36 (1.2-1.63)	 2.1 P=0.13	
BMI Mean ± SD Median (range)	 16.5± 2.5 17.19 (9.17-19.58)	 14.9±2.9 15.5 (9.47-19.9)	 20.8± 1.8 20.3 (16.67-25.8)	 39 P=0.0001	(0.06)* (0.0001)** (0.0001)***
Systolic blood pressure Mean ± SD Median (range)	 106±9.7 100 (100-1 20)	 106.5±7.2 110 (95- 120)	 107.5±4.7 110 (100-115)	 0.28 P=0.75	
Diastolic blood pressure **Mean ± SD** **Median** **(range)**	 69.3±5.1 70 (60- 80)	 70.3±6.9 70 (60-80)	 65.2 ±5.9 65 (60-80)	 4.6 P=0.015	(0.64)* (0.04)** (0.008)***

(Comparison good and bad control diabetes children)*, (Comparison of good control diabetic and healthy children)**, (Comparison of bad control diabetic and healthy children)***.

There was significant higher value of HBA1c, RBS, cholesterol level, triglycerides level, LDL level of bad control diabetic children compared to good control diabetic children and healthy control children. Also, there was significant higher value of HBA1c, RBS, cholesterol level, and triglycerides level of good control diabetic children compared to healthy control children. **(Table 4).**

Table (4): Sugar and Lipid profiles of studied groups

Variables	Good control diabetes children (n.14)	Bad control diabetes children (n.16)	Healthy control (n.30)	F	Post hoc test
Glycosylated hemoglobin (HBA1c) Mean ± SD Median (range)	 6.7±0.57 6.9 (5.6-7.4)	 9.3±0.82 9.5 (7.8-10.5)	 4.7±0.37 4.8 (4-5.2)	 F=324 0.0001	(0.0001)* (.0001)** (.0001)***
Random blood sugar Mean ± SD Median (range)	149.8±30.5 152.5 (100-227)	264.5±111 227 (160-533)	94.9±10.3 98 (78-110)	F=47.3 0.0001	(0.0001)* (.006)** (.0001)***.
Variables	**Good control diabetes children (n.14)**	**Bad control diabetes children (n.16)**	**Healthy control (n.30)**	**F**	**Post hoc test**
Cholesterol level :N (150-250 mg/dl) **Mean ± SD**	161±8	175.5±26.4	138.4±30.9	7.6 0.001	(0.21)* (0.03)** (0.0001)***
Triglycerides level :N (50-190 mg/dl) **Mean ± SD**	 114.6±8.9	 116.6±5.5	 85.5±4.9	KW =8.8 0.012	(0. 91)* (0.042)** (0.024)***
HDL level :N (40-60 mg/dl) **Mean ± SD**	 42.3±6.9	 43.8±8.2	 43.6±1.2	0.11 0.68	-
LDL level :N (<180 mg/dl) **Mean ± SD**	 90.4±5.8	 107.3±3.6	 84.1±6.1	 3.6 0.033	(0.1)* (0.49)** (0.009)***

There was significant higher value of following echocardiography measures: LVIDs, LVIDd, LVId, LVIsd, PWD S, PWD D, RWT, LVMI, LVM both of bad and good control diabetic children compared to healthy control **(Table 5).**

Table (5): Echocardiography measures of studied groups

	Good control diabetes children n.14	Bad control diabetes children n.16	Healthy children n.30	F/KW	Post hoc test
LVIDs (cm) Mean ± SD	2.46±0.41	2.53±0.44	1.53±0.31	51.3 0.0001	(0.61)* (0.0001)** (0.0001)***
LVIDd (cm) Mean ± SD	3.46±0.5	3.74±0.7	2.66±0.12	9.8 0.007	(0.33)* (0.037)** (0.005)***
IVSd (Cm) Mean ± SD	0.75±0.17	1.1±0.02	0.73±0.15	8.965 0.01	0(.03.)* (0.41.)** (0.004)***
PWD S (Cm) Mean ± SD	1.1±0.25	1.16±0.17	0.91±0.13	F 6.4 0.003	(0.48)* (0.02)** (0.002)***
PWD D (Cm) Mean ± SD	0.77 ±0.19	0.92±0.23	0.7±0.15	9.9 0.007	(0.058)* (0.13)** (0.0001)***
EF% Mean ± SD	68.7±6.6	71.2±9.95	75.7±11.7	F 2.1	0.09
FS% Mean ± SD	41.2±6.9	41.4±2.9	43.5±2.2	.865 0.65	0.649
RWT (Cm) Mean ± SD	0.48±0.12	0.54±0.19	0.37±0.039	13.8 0.001	(0.31)* (0.026)** (0.004)***
LVMI g/m^2 Mean ± SD	65±6.2	100±5.3	28.3±5.9	35.4 0.0001	(0.0001)* (0.0001)** (0.0001)***
LVM (g) Mean ± SD	73.2±5.4	121.7±6.1	28.2±1.4	37.13 0.0001	(0.0001)* (0.0001)** (0.0001)***

EF%: ejection fraction, **F= ANOVA test**, **FS%:** Fraction shortening, **IVSd:** interventricular septal dimension, **KW=Kruskall-Wallius test**, **LVIDd:** Left ventricular dimension diastole, **LVIDs:** Left ventricular dimension systole, **LVM :** left ventricular mass, **LVMI :** left ventricular mass index, **PWDD:**posterior wall dimension diastole, **PWDS:**posterior wall dimension systole, **RWT:** Relative wall thickness, **SD=standard deviation**

(Comparison good and bad control diabetes children)*, (Comparison of good control diabetic and healthy children)**, (Comparison of bad control diabetic and healthy children)***.

There was significant higher value of IL-27 of bad control diabetic children compared to both good control diabetic children and healthy children **(Table 6).**

Table (6): Serum interleukin 27 of studied groups

	Good control diabetes children n.14	Bad control diabetes children n.16	Healthy control n.30	Kw	Post hoc test
Serum Interleukin 27(ng/L) Mean ± SD	273.1±6.2	688.4±66.4	286.6±6.8	7.6 P=0.023	(0.01)* (0.15)** (0.017)***

KW=Kruskall Wallius test, SD=standard deviation

(Comparison good and bad control diabetes children)*, (Comparison of good control diabetic and healthy children), (Comparison of bad control diabetic and healthy children)*****

DISCUSSION

Children with (T1DM) are at the highest risk for developing early cardiovascular disease. Many studies have shown that the number and severity of risk factors affect the amount of atherosclerosis in children's blood vessels. T1DM results in endothelial dysfunction and early atherosclerosis, which can lead to coronary artery disease and other micro- and macrovascular problems before their time [12].

One of the cytokines in the superfamily of interleukin-6 and interleukin-12. Rheumatoid arthritis, multiple sclerosis, and inflammatory bowel disease are just a few of the autoimmune illnesses in which IL-27 has been found to have pro- and anti-inflammatory effects. There are more than 50 genetic loci that have been related to T1D in humans, and one of these is on chromosome 16 and comprises 24 protein-coding genes, including IL27, which encodes the p28 subunit [13, 14].

Studies of IL-27 in adult with diabetes mellitus were performed but studies in children are few, so the purpose of this study is to evaluate serum concentration IL-27 and echocardiography finding with T1DM. To our knowledge, this is the first study evaluating the level of serum concentration IL-27 in children and adolescents with T1DM.

Our results demonstrated that there was not statistically difference between type I diabetes children and healthy control regarding to sex and age ensuring matching of the groups.

Both genetic susceptibilities and shared surroundings, including cultural elements like values and perspectives and behavioral aspects like nutrition and physical exercise, are reflected in a family history [15]. More than one half (53.3%) of diabetic cases have positive family history with significant difference with control group. Similarly, **Alghobashy *et al.*** [16] detected significant difference regarding family history. Having a family history of diabetes and hypertension in children type 1 diabetes are substantial risk factors for cardiovascular disease.

Regarding clinical characters of type 1 diabetic children, the age at disease onset ranged from 2 – 12.4 years old with mean 7.3±3.14 years old. Duration of disease ranged from 1-10 years with mean 3.5±2.5 years. **Christoforidis *et al.*** [17] found that the mean age at the time of the diagnosis of T1DM was 6.23 ± 3.43 years and the mean duration of T1DM was 2.48 years. **Zhang *et al.*** [18] showed that the mean duration of T1DM was 4.7 ± 2.4 years.

Almost our children with T1DM treated with long-acting insulin with dose range from 10 units to 72 units. 46.7% of type1 diabetic children had good control. **Pickup and Renard** [19] found that type T1DM children using long-acting insulin are well controlled and do not have problems of hypoglycemia.

In the current study, there was significant higher value of weight, BMI of healthy control children compared to type I diabetic children while there was no significant difference regarding height. Similarly, **Snell-Bergeon *et al.*** [20] found that BMI was significantly lower, and obesity was less prevalent, in participants with type 1 diabetes compared with controls. However, **Alghobashy *et al.*** [16] **and MacKenzie *et al.*** [21] found that there was significant lower value of BMI of healthy control children compared to type I diabetic children while there was no significant difference regarding height.

People with DM are more likely to suffer from hypertension. Obesity, insulin resistance, and/or hyperinsulinemia are usually blamed for the strong connection between diabetes and hypertension. Changes in blood vessel function and structure that result from hyperglycemia may also contribute to hypertension [22]. In the present study, there was significant higher value of (DBP) of type I diabetic children compared to healthy control children while there was no significant difference regarding SBP. **Garg *et al.*** [23] found that mechanisms inherent in the diabetes condition, such as hyperglycemia, extracellular fluid expansion, modifications in atrial natriuretic peptide, and the renin-angiotensin system, could be responsible for the elevation in blood pressure. In agreement with our study, **Sivieri *et al.*** [24] revealed higher DBP in type 1 diabetic patients than nondiabetic subjects.

Glycosylated hemoglobin (HBA1c) is a gold standard of glycemic control in patients with T1DM. There was significant higher value of HBA1c, and RBS of bad control diabetes children compared to both good control diabetic children and healthy control children. Also, there was significant higher value of HBA1c, and RBS of good control diabetes children compared to healthy control children. In addition, **Alghobashy *et al.*** [16] and **Zhang *et al.*** [18] demonstrated that the T1DM group had significantly higher glucose and HbA1c levels compared to the control group.

Diabetes is often accompanied by undiagnosed dyslipidemia, increase in (TG), (LDL-C), and a decrease in (HDL-C). Regarding lipid profile, there was significant higher value of cholesterol level, triglycerides level, LDL level of bad control and good control diabetic children compared to healthy control children. Also, the values were higher in bad control than good control diabetes children but without significant difference. While there was no significant difference regarding HDL among the studied groups. **Vergès** [25] found that quantitative lipid abnormalities are observed in T1DM patients with poor control as a result of insulin deficiency leading to hypertriglyceridemia. In agreement with our study, **Snell-Bergeon *et al.*** [20] found that participants with type 1 diabetes had higher total cholesterol than the healthy controls.

Effect of DM on cardiac dimensions is believed to be a multifactorial disease. In the present study there were significant higher values of following echocardiography measures: IVSD, LVIDs, LVIDd, LVId, LVIsd, PWD S, PWD D, RWT, LVMI, LVM among diabetic versus control. While there was no significant difference regarding EF and FS. Using conventional echocardiographic parameters or tissue Doppler, research in children and adolescents with Type 1 Diabetes (T1D) reported varying results on subclinical LV diastolic dysfunction. Subclinical systolic longitudinal dysfunction has also been found in adults and adolescents with T1D using tissue Doppler imaging studies [(26)]. In agreement with our study, **Weber *et al.*** [(27)] found that there was significant increase in LVIDs in diabetic patients than control group. **Rakha and Aboelenin** [(28)] found that there was significant increase in PWD in diabetic patients than control group while there was no significant difference in EF and FS among the studied groups.

The increased IL-27 function directly affect the downstream signaling pathway, and it could have effects on T1D pathogenesis. Regarding IL-27 value, there was significant higher value of IL-27 of bad control diabetic children compared to both: good control diabetic children and healthy children. But there was no significant difference between good control diabetes children and healthy control children. **Ciecko *et al.*** [(11)] found that IL-27 was increased in T1D. According to a prior study, mice transgenically overexpressing IL-27 showed increased islet inflammation and CD8 T-cell responses, which supports the significance of IL-27 in T1D [(29)]. **Łukawska-tatarczuk *et al.*** [(30)] found that levels of IL-27 were non-significantly higher in adult T1D compared to controls. This difference may be due to different population and inclusion and exclusion criteria.

CONCLUSION

T1D is associated with elevation of IL-27 levels and lipid profile. This association is more evident in poorly controlled patients indicating a relevant role of IL- 27 and dyslipidemia on the pathogenesis of the disease.

There is a difference in the parameters of echocardiography with increase cardiac dimensions in T1D when compared to controls, which may denote a subtle reduction in cardiac function in these patients and possible incipient diabetic cardiomyopathy.

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Author contribution: Authors contributed equally in the study.

REFERENCES

1. **Rawshani A, Rawshani A, Gudbjörnsdottir S (2017b):** Mortality and cardiovascular disease in type 1 and type 2 diabetes. N Engl J Med., 377(3):300-301.
2. **Glovaci D, Fan W, Wong N (2019):** Epidemiology of diabetes mellitus and cardiovascular disease. Curr Cardiol Rep., 21:1-8.
3. **Wang Y, O'Neil A, Jiao Y *et al.* (2019):** Sex differences in the association between diabetes and risk of cardiovascular disease, cancer, and all-cause and cause-specific mortality: A systematic review and meta-analysis of 5,162,654 participants. BMC Med., 17: 1–18.
4. **Ohkuma T, Komorita Y, Peters S *et al.* (2019):** Diabetes as a risk factor for heart failure in women and men: A systematic review and meta-analysis of 47 cohorts including 12 million individuals. Diabetologia, 62: 1550–1560.
5. **Sousa G, Pober D, Galderisi A *et al.* (2019):** Glycemic control, cardiac autoimmunity, and long-term risk of cardiovascular disease in type 1 diabetes mellitus. Circulation, 139: 730–743.
6. **Cosentino F, Grant P, Aboyans V *et al.* (2019):** 2019 ESC guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. Eur Heart J., 41: 255–323.
7. **Wang Q, Liu J (2016):** Regulation and immune function of IL-27. Adv Exp Med Biol., 941: 191–211.
8. **Jørgensen P, Biering-Sørensen T, Mogelvang R *et al.* (2019):** Predictive value of echocardiography in type 2 diabetes. Eur Heart J Cardiovasc Imaging, 20(6):687-693.
9. **Carpenter M, Sinclair H, Kunadian V (2016):** Carotid intima media thickness and its utility as a predictor of cardiovascular disease: a review of evidence. Cardiol Rev., 24(2):70-75.
10. **Shahi A, Afzali S, Salehi S *et al.* (2020):** IL-27 and autoimmune rheumatologic diseases: The good, the bad, and the ugly. Int Immunopharmacol., 84: 1-5.
11. **Ciecko A, Foda B, Barr J *et al.* (2019):** Interleukin-27 is essential for type 1 diabetes development and Sjögren syndrome-like inflammation. Cell Rep., 29(10): 3073–3086.
12. **Chen C, Cifra B, Morgan G *et al.* (2016):** Left ventricular myocardial and hemodynamic response to exercise in young patients after endovascular stenting for aortic coarctation. J Am Soc Echocardiogr., 29:237–246.
13. **Evangelou M, Smyth D, Fortune M *et al.* (2014):** A method for gene-based pathway analysis using genomewide association study summary statistics reveals nine new type 1 diabetes associations. Genet Epidemiol., 38: 661–670.
14. **Fortune M, Guo H, Burren O *et al.* (2015):** Statistical colocalization of genetic risk variants for related autoimmune diseases in the context of common controls. Nat Genet., 47: 839–846.
15. **Kuo C, Chou I, Grainge M *et al.* (2018):** Familial aggregation and heritability of type 1 diabetes mellitus and coaggregation of chronic diseases in affected families. Clin Epidemiol., 10: 1447-1455.

16. **Alghobashy A, Shokry D, Gawish H (2013):** Interleukin-12 levels in Egyptian children with type 1 diabetes mellitus. Egyptian J Pediatri Allergy and Immunol., 11(1):41-45
17. **Christoforidis A, Kavoura E, Nemtsa A *et al.* (2020):** Coronavirus lockdown effect on type 1 diabetes management on children wearing insulin pump equipped with continuous glucose monitoring system. Diabetes Res Clin Pract., 166: 1-7.
18. **Zhang Y, Zhang H, Li P (2019):** Cardiovascular risk factors in children with type 1 diabetes mellitus. J. Pediatr. Endocrinol Metab., 32(7): 699-705.
19. **Pickup J, Renard E (2008):** Long-acting insulin analogs versus insulin pump therapy for the treatment of type 1 and type 2 diabetes. Diabetes Care, 31(2): 140-145.
20. **Snell-Bergeon J, West N, Mayer-Davis E *et al.* (2010):** Inflammatory markers are increased in youth with type 1 diabetes: the SEARCH Case-Control study. J Clin Endocrinol Metab., 95(6):2868-2876.
21. **MacKenzie K, Wiltshire E, Peña A *et al.* (2009):** Hs-CRP is associated with weight, BMI, and female sex but not with endothelial function in children with type 1 diabetes. Pediatri Diabetes, 10(1): 44-51.
22. **De Boer I, Kestenbaum B, Rue T *et al.* (2008):** Insulin therapy, hyperglycemia, and hypertension in type 1 diabetes mellitus. Arch Intern Med., 168(17): 1867-1873.
23. **Garg S, Chase H, Rothman R *et al.* (1997):** 24-hour ambulatory blood pressure and renal disease in young subjects with type 1 diabetes. J Diab Compli., 11:263–267.
24. **Sivieri R, Deandrea M, Gai V *et al.* (1994):** Circadian blood pressure levels in normotensive normoalbuminuric type 1 diabetic patients. Diabet Med., 11:357–361.
25. **Vergès B (2020):** Dyslipidemia in type 1 diabetes: a masked danger. Trends Endocrinol Metab., 31(6): 422-434.
26. **Ozdemir O, Koksoy A, Bulus A *et al.* (2016):** The effects of type 1 diabetes mellitus on cardiac functions in children: evaluation by conventional and tissue Doppler echocardiography. J Pediatr Endocrinol Metab., 29(12): 1389- 1395.
27. **Weber T, da Silva R, Cossul S *et al.* (2021):** Echocardiographic evaluation in type 1 diabetes mellitus. Revista Portuguesa de Cardiologia., 40(10): 757-765.
28. **Rakha S, Aboelenin H (2019):** Left ventricular functions in pediatric patients with ten years or more type 1 diabetes mellitus: Conventional echocardiography, tissue Doppler, and two-dimensional speckle tracking study. Pediatri Diabetes, 20(7): 946-954.
29. **Wojno E, Hosken N, Stumhofer J *et al.* (2011):** A role for IL-27 in limiting T regulatory cell populations. J. Immunol., 187: 266–273.
30. **Łukawska-Tatarczuk M, Franek E, Czupryniak L *et al.* (2021):** Sirtuin 1, visfatin and IL-27 serum levels of type 1 diabetic females in relation to cardiovascular parameters and autoimmune thyroid disease. Biomolecules, 11(8): 1-17.