GSC Advanced Research and Reviews

eISSN: 2582-4597 CODEN (USA): GARRC2

Cross Ref DOI: 10.30574/gscarr

Journal homepage: https://gsconlinepress.com/journals/gscarr/

(RESEARCH ARTICLE)

Check for updates

Correlation between HbA1c levels and left ventricular function in children with Type 1 Diabetes Mellitus

Desmiyati Natalia Adoe *, Ni Putu Veny Kartika Yantie, Made Sukmawati, Ida Bagus Subanada, Made Gede Dwi Lingga Utama and I Made Arimbawa

Departement of Child Health, Medical Faculty of Udayana University, Prof Dr. I.G.N.G. Ngoerah Hospital, Denpasar, Bali, Indonesia.

GSC Advanced Research and Reviews, 2023, 17(03), 093–100

Publication history: Received on 28 October 2023; revised on 13 December 2023; accepted on 15 December 2023

Article DOI: https://doi.org/10.30574/gscarr.2023.17.3.0457

Abstract

Background: Diabetic cardiomyopathy is one of the macrovascular complications in type 1 diabetes mellitus (T1DM). Left ventricular dysfunction primarily reflects diastolic dysfunction which is early sign of diabetic cardiomyopathy. Improved glycemic control can delay the onset and progression of this complication. An important indicator of long-term glycemic control is glycosylated hemoglobin (HbA1c).

Objective: The aim of this study is to evaluate the correlation between HbA1c levels with left ventricular diastolic function in children with T1DM.

Methods: This study was an observational study with cross-sectional design in children aged 1 month-18 years with T1DM, at Prof Dr. I.G.N.G. Ngoerah Hospital, Denpasar from November 2019–September 2021, using consecutive sampling. Glycosylated hemoglobin (HbA1c) was meassured by blood samping and LV function was assessed by using tissue Doppler imaging (TDI). Statistical analysis was done by Pearson and Spearman correlation test. A p-values of <0.05 was considered statistically significant.

Results: A total of 36 subjects were recruited in this study. There was a low positive correlation between HbA1c levels with E/e' ratio (r=0.284, p=0.047), and MPI (r=0.358, p=0.020). After adjusting body mass index and duration of T1DM as confounding variables, we found a low positive correlation between HbA1c levels and E/e' ratio (r=0.325, p=0.030), MPI (r = 0.390, p=0.020).

Conclusion: HbA1C has a positive correlation with left ventricular diastolic function in children with T1DM.

Keywords: HbA1c; Left ventricular function; Type 1 diabetes; Children

1. Introduction

Type 1 diabetes mellitus (T1DM) is one of the most common endocrine and metabolic conditions in childhood, characterized by chronic hyperglycemia due to pancreatic beta-cell damage [1]. The prevalence of T1DM has increased by 2-5% every year. In Indonesia, the incidence of T1DM is 0.3 per 10.000 children, which there are two peaks of incidence, namely at the age of 5-6 years and 11 years [2]. Poor glycemic control can cause complications of T1DM that can affect the function of organ systems [2,3]. The long-term complications of T1DM mainly included microvascular and macrovascular complications. One of the macrovascular complications in T1DM is diabetic cardiomyopathy [2,3,4].

* Corresponding author: Desmiyati Natalia Adoe

The alteration of myocardial function induced by diabetes mellitus begin earlier than generally thought, and these changes may be accelerated when glycemic control is poor. Patients with T1DM may have deterioration of left ventricular (LV) function despite the absence of further concomitant cardiac problems[5]. The most frequent and earliest detectable functional abnormality in dilated cardiomyopathy (DCM) is diastolic dysfunction [4,5,6].

Echocardiography is a non-invasive method used to diagnose diabetic cardiomyopathy or diabetes-induced myocardial dysfunction. Tissue Doppler imaging (TDI) is a modal of echocardiography that has proven to be more useful to evaluate ventricular filling in diabetes patients. Presently, the ratio of early diastolic mitral inflow velocity to early diastolic mitral annulus velocity (E/e' ratio) is used for the evaluation of LV filling pressure, and it has been used as a marker to diagnose diastolic dysfunction. Myocardial Performance Index (MPI/Tei Index), which includes both systolic and diastolic time intervals to assess the global cardiac dysfunction, was found to provide important prognostic information for the risk of future congestive heart failure beyond other measurements of cardiac function [7-10].

Studies to evaluate the use of TDI in detection of cardiac dysfunction in children with T1DM are few and conflicting [8-12]. Whereas study about the correlation between HbA1c levels and MPI is still rarely done. To the best of our knowledge, no study to date has been conducted on the correlation between HbA1c levels and MPI in Indonesia. Early detection of left ventricular diastolic dysfunction in T1DM children must be done to prevent further cardiovascular complications and it is expected to reduce morbidity and mortality in T1DM children. Therefore, we ought to analyze the correlation of HbA1c levels with left ventricular diastolic function in children with TIDM.

2. Method

This was an observational study with cross-sectional design. This study was conducted at the Department of Child Health in Prof Dr. I.G.N.G. Ngoerah Hospital, Denpasar, Bali, from November 2019 to September 2021. The inclusion criteria were T1DM patient aged 1 month to 18 years old, whom were willing to participate in the study and provided informed consent. Patients with concomitant illness affecting cardiac function, consuming heart medications, hypertension, chronic infection, acute or chronic kidney failure, thyrotoxicosis, underwent chemotherapy, and severe anemia were excluded. Samples were collected by using consecutive sampling. The minimum sample size was 36 subjects.

The patient had their history taken and explained about the examination. Informed consent was obtained from all parents of patients. The examination including cardiac examination, blood pressure (BP) measurement, electrocardiogram, and blood sampling, as well as echocardiography were performed. HbA1c level was determined using ion-exchange HPLC method [2]. Left ventricular diastolic function was observed using two-dimensional echocardiography. A TDI examination of the left ventricle was conducted by placing the PW Doppler sample volume over the portion of mitral annulus, close to the posterior wall of the left ventricle, in the apical four-chamber view.

The following parameters were measured: ejection fraction, tricuspid annular plane systolic excursion (TAPSE), peak early filling velocity (E), peak late atrial filling velocity (A), E/A ratio, deceleration time of E velocity (DT), isovolumic relaxation time (IVRT), and early peak velocities of mitral annulus (e'). Thus, E/e' ratio and LV MPI were calculated. Two pediatric cardiologist consultants interpreted the electrocardiography and echocardiography results.

Data were calculated using the statistic method, i.e., mean, standard deviation, and normality test using Shapiro Wilk Test. Spearman's and Pearson correlation tests were used to assess the correlation between parameters. A p-value of < 0.05 was considered statistically significant. Body mass index and duration of T1DM were considered as confounding factors that were adjusted using Pearson's partial correlation analysis. This study was approved by Research Ethics Committee of the Faculty of Medicine, Udayana University/Sanglah General Hospital.

3. Result

During the study period, a total of 38 patients with T1DM were eligible; however, only 36 subjects were finally analyzed due to two subjects being unwilling to participate. In this study, the median age was 13.96 years and most of the subjects were female (22 subjects). The predominance of diabetes duration was less than 4 years in 23 subjects with median of 2.8 years. This study found that the mean HbA1c level was 9.51 ±2.88 %. The detailed baseline characteristics of subjects included in this study are shown in Table 1.

Table 1 Characteristics of subjects

Variable	Value (n=36 subjects)
Age, median (range), years	13.96 (3-18)
Gender, n (%)	
Female	22 (61.1)
Body Mass Index, mean (SD), kg/m^2	19.4 (4.79)
Nutritional status, n (%)	
Severly wasted	1 (2.8)
Wasted	7 (19.4)
Well-nourished	14 (38.9)
Overweight	6 (16.7)
Obese	8 (22.2)
Age at diagnosis of DM, mean (SD), years	9.33 (3.93)
Diabetes duration, median (range), years	2.8 (0.1-11)
Hemoglobine Level, mean (SD), g/dL	12.98 (1.45)
Systolic blood pressure, median (range), mmHg	100 (80-120)
Diastolic blood pressure, median (range), mmHg	70 (60-90)
HbA1c Levels, mean (SD), g/dL	9.51 (2.88)
Cardiac functional status, n (%)	
NYHA 1	25 (69.4)
NYHA 2	9 (25)
NYHA 3	2 (5.6)
NYHA 4	0 (0)
Electrocardiogram characteristics, n (%)	
Normal sinus rhythm	16 (44.4)
Prolonged QTc interval	18 (50)
Left ventricular hypertrophy	2 (5.6)
Echocardiography characteristics Ejection fraction, mean (SD), %	 71.47 (6.55)
TAPSE (cm), mean (SD), cm	2.12 (0.33)
E/A ratio, median (range)	1.50 (1.0-2.4)
E/e' ratio, mean (SD)	6.94 (1.31)
MPI, median (range)	0.63 (0.32-1.46)

SD: Standard deviation, NYHA: New York Heart Association, TAPSE: Tricuspid annular plane systolic excursion, MPI: Myocardial performance index

The Pearson correlation test revealed a significantly low positive correlation between HbA1c levels and E/e' ratio (r=0.284, p=0.047). A low positive correlation was observed between HbA1c level and MPI (r=0.358, p=0.020) (Spearman's correlation test). Correlation of HbA1c levels with E/e' Ratio and MPI was shown in Table 2.

Table 2 Correlation of HbA1c levels with E/e' Ratio and Myocardial Performance Index

Variable	HbA1c	
	Correlation Coefficient	p-value
E/e' ratio	0.284	0.047
MPI	0.358	0.020

After adjusting for confounding variables (body mass index and duration of diabetes), a partial correlation analysis showed a significant low correlation between HbA1c levels and E/e' ratio (r=0.325, p=0.030), and also a significant low correlation between HbA1c levels and MPI (r = 0.390, p=0.020) (Table 3).

Table 3 Partial correlation between HbA1c with E/e' Ratio and MPI after adjusting the confounding variables

Variable	Adjusting	HbA1c	
		Correlation Coefficient	p-value
E/e' ratio	BMI and duration of diabetes	0.325	0.030
MPI		0.390	0.020

4. Discussion

Type 1 diabetes melitus (T1DM) is one of the most common chronic diseases of childhood that has an increasing incidence by more than seven times from 3.88 to 28.19 per 100,000 population in 2000 and 2010 [13]. Data fom The Indonesian Pediatrician Association showed that 1220 children with T1DM dominated by group age 10-14 year old in 2018 [14]. In this study, the mean age at the time of diagnosis DM was 9.33 ± 3.93 years, with the highest proportion of children aged of 10-14 years as many as 16 subjects (44.4%). Similar results were also reported by and Dabalea et al.15 and Kim et al [16].

Glycated hemoglobin (HbA1c) is an important indicator of long-term glycemic control and can describe the cumulative glycemic history of the preceding two to three months. The Indonesian Pediatrician Association recommends target HbA1c less than 7.5% in T1DM patients. HbA1c more than 7.5% indicate poor glycemic control [1,2]. In this study, the mean HbA1c levels among the participants was 9.51 ± 2.88%, which is higher than the recommended target. This result was in line with a study by Bakhoum et al [8]. that found the mean HbA1c levels was 9.77 ± 1.42%. Another study by Indriyani and Adji [17] reported that 18 of 28 children with T1DM had HbA1c more than 9%. Wulandari [18] also reported that 73% of 26 children with T1DM had HbA1c levels more than 7.5%.

This study revealed that most of subjects were adolescents and females (61.1%). Adolescents tend to have poor glycemic control due to the hormonal changes that can induce insulin resistance. The pubertal growth spurt induced by steroid and pubertal growth hormone, both of which counteract insulin's effects, in conjunction with the pubertal peak. Insulin sensitivity can decrease at the beginning of puberty and then retrieve to normal after completing somatic growth and sexual maturation [18,19]. Some studies also revealed that the HbA1c level was significantly higher in female patients [18,20,21]. Possible reason might be due to hormonal factors and psychological problems. These conditions can affect the treatment effectiveness and are frequently associated with poor glycemic control. Females have higher body fat and hypertropic adipose cell. It has been associated to higher levels of leptin, that thought to play some role in insulin resistance and induce poor glycemic control [21,22].

Cardiovascular disease risk remains significantly high in T1DM patients. Diabetic cardiomyopathy is characterized by myocardial dilatation and hypertrophy, as well as decrease in the systolic and diastolic function of the left ventricular (LV). The LV function was impairment before the clinical signs of congestive heart failure manifest. Diastolic dysfunction has been identified as an early sign of diabetic cardiomyopathy preceding systolic impairment [23]. Left ventricular diastolic dysfunction can be determined by calculated E/e' ratio and MPI. E/e' ratio has been considered and proven to be effective in determining left ventricular filling pressure[24]. In present study, the average E/e' ratio was 6.94 ± 1.31. In line with a study carried out by Ali et al.[9] found that the average E/e' septal ratio was 6.9± 1.6 and E/e' lateral ratio was 6.4± 1.7. Otherwise, a previous study by Bruvand et al.[25] revealed a higher E/e' ratio of 8.1 ± 1.6. This discrepancy

may be associated with the differences in diabetes duration. Bruvand et al [25] studied in 146 T1DM patients revealed average diabetes duration of 5.6 ± 1.6 years. In this study, the median diabetes duration was 2.8 years (range 0.1-11 years). Left ventricular diastolic dysfunction can be independently associated with diabetes duration. The longer the duration of diabetes can increase LV diastolic dysfunction and increased risk of cardiovascular disease [26].

Poor glycemic control was associated left ventricular diastolic dysfunction[10]. Our results demonstrated a significant positive correlation between HbA1c levels and E/e' ratio ($r=0.284$, $p=0.047$). A previous study by Shishehbor et al. [12] reported a strong positive correlation between E/e' ratio and HbA1c levels in 25 adult patients with T1DM ($r=0.68$ and $p<0.05$). On the contrary, different research by Gul et al. [26] showed no significant correlation between HbA1c levels and E/e' ratio ($p>0.05$). Ali et al. [9] also reported a very weak positive correlation between HbA1c levels and the E/e' ratio ($r=0.10$ and $p>0.05$). The difference result might be partly explained by the differences in glycemic control among participants. In this study, 22 of 36 study participants (72.2%) had poor glycemic control, whereas study by Ali et al [.9] revealed that most subjects had good glycemic control (58.7%).

In this study, we found that the median MPI was 0.63 (range 0.32-1.46). Similarly, Salem et al. [24] reported that the mean MPI in TIDM children was 0.57 ± 0.15 [24]. Study by Bakhoum et al. [8] also found similar result (0.58 ± 0.18). Our results demonstrated a positive correlation between HbA1c levels and LV MPI ($r=0.358$, $p=0.020$). A previous study by Pattoneri et al.[27] in Type 2 DM revealed significant correlation between HbA1c levels and MPI ($r=0.37$ and $p<0.01$).

MPI was associated with left ventricular performance in the early stages of heart failure [27]. A higher MPI values show increase of IVRT and IVCT, also decrement of ejection time. The isovolumic contraction time (IVCT) reflects the time when calcium enters the myoplasm from the sarcolemma, while isovolumic relaxation time reveals the removal of Ca^{2+} from the myoplasm by Ca^{2+}-ATPases. Most of the abnormal myocardial contractility and relaxation appears to be caused by changes in cellular Ca^{2+} processing in the myocardium, which was impaired in DM patients [8].

The partial correlation test revealed a statistically significant positive correlation between HbA1c levels and E/e' ratio ($r=0.325$, $p=0.030$), left ventricular MPI ($r=0.390$, $p=0.015$) while controlling for BMI and diabetes duration. Changes in left ventricular diastolic function are common with increasing BMI. The heart adapts to chronic volume overload in obese patients. This condition will result in structural changes such as eccentric hypertrophy and abnormalities in diastolic function in the early stages [28].

Body mass index was also associated with glycemic control in T1DM patients. Adequate insulin therapy can reduce glycosuria, increase appetite and metabolism of T1DM. Thus, it can induce weight gain [29,30]. In T1DM, weight gain during insulin therapy might be considered as a normalization of lost weight and associated with improved glycemic control. A lower BMI may indicate low glucose utilization, inadequate insulin therapy, and poor glycemic control [30]. Our study found that the mean BMI was 19.4 ± 4.79 kg/m2. This result is in accordance with Abd-El Aziz et al. [31] that found mean BMI of 19.29 ± 2.7 kg/m2 among the T1DM children. A higher BMI can indicate excess energy stored as fat tissue, causing central obesity [32]. Increased abdominal visceral fat can increased free fatty acids, triggering a state of hyperinsulinemia, increased glucose production by the liver, and induced hypertriglyceridemia. This condition can adversely affect glycemic control and increase the risk of macrovascular complications in T1DM [29,30,32].

The duration of T1DM can impact the LV diastolic function. In this study, we found the median diabetes duration was 2.8 years (range 0.1-11 years). Adal et al. [33] reported that the longer diabetes duration had lower E/A ratio and longer IVRT than those with shorter diabetes duration. A study by Kim and Kim [10] also found an association between diabetes duration more than four years and LV diastolic dysfunction in T1DM. Early detection of heart function can prevent macrovascular complications in T1DM. The International Society for Pediatric and Adolescent Diabetes (ISPAD) recommends screening of macrovascular complications in T1DM aged more than 11 years with diabetes duration for 2-5 years. Initial screening can be done by regularly measuring the blood pressure and conducting lipid profile examinations every two years. Early detection needs to be done if there is a family history of hypercholesterolemia and cardiovascular disease [34].

The limitations of this study were non-homogeneous diabetes duration and not determined the lipid profile. Therefore, we could not rule out dyslipidemia as one of the factors that correlated with left ventricular diastolic dysfunction. In further research, it is possible to consider BMI, duration of diabetes, and examining lipid profiles. Thus, it is expected to obtain more representative correlation results.

5. Conclusion

In conclusion, HbA1c has a significant and positive correlation with E/e' rasio and MPI in children of T1DM. The early detection of LV diastolic dysfunction must be performed to prevent cardiovascular risk and also to reduce morbidity and mortality rates in children with T1DM.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

Statement of informed consent

Informed consent was obtained from parents of participants included in the study.

References

[1] Rustama DS, Yati NP, Andriana N, Pulungan AB. Diabetes Mellitus. Dalam: Batubara JRL, Tridjaja B, Pulungan AB, penyunting. Buku Ajar Endokrinologi Anak. Edisi Kedua. Jakarta: Badan penerbit IDAI. 2018; p. 146-206.

[2] Tridjaya B, Yati NP, Faizi M, Marzuki ANS, Moelyo AG, Soesanti F. Konsensus Nasional Pengelolaan Diabetes Melitus Tipe-1 di Indonesia. Edisi ketiga. Jakarta: Badan Penerbit IDAI. 2015; p.1-10.

[3] Himawan IW, Pulungan AB, Tridjaja B, Batubara TJ. Komplikasi Jangka Pendek dan Jangka Panjang Diabetes Melitus Tipe 1. Sari Pediatri. 2008;10(6):367-72. DOI: 10.14238/sp10.6.2009.367-72.

[4] Boudina S, Abel D. Diabetic cardiomyopathy revisited. Circulation. 2007;115:3213-23. DOI: https://doi.org/10.1161/CIRCULATIONAHA.106.679597

[5] Trost S, LeWinter M. Diabetic cardiomyopathy. Curr Treat Options Cardiovasc Med. 2001;3:481–92.

[6] Voulgari C, Papadogiannis D, Tentolouris N. Diabetic cardiomyopathy: from the pathophysiology of the cardiac myocytes to current diagnosis and management strategies. Vasc Health Risk Manag. 2010;6:883-903. DOI: https://doi.org/10.2147/VHRM.S11681

[7] Sharifov OF, Schiros CG, Aban I, Denney TS, Gupta H. Diagnostic Accuracy of Tissue Doppler Index E/e' for evaluating left ventricular filling pressure and diastolic dysfunction/heart failure with preserved ejection fraction: a systematic review and meta-analysis. J Am Heart Assoc. 2016;5(1):e002530. DOI: https://doi.org/10.1161/JAHA.115.002530

[8] Bakhoum SW, Habeeb HA, Elebrashy IN, Rizk MN. Assessment of left ventricular function in young type 1 diabetes mellitus patients by two-dimensional speckle tracking echocardiography: relation to duration and control of diabetes. The Egyptian Heart Journal. 2016;68(4):217-25. DOI: https://doi.org/10.1016/j.ehj.2016.02.006

[9] Ali BAM, Babrs GMM, Ahmed HTT, Ahmed AKI. Assesment of ventricular dysfunction in children with type 1 diabetes mellitus (T1DM). Curr Pediatr Res. 2017;21(2):306-12.

[10] Kim EH, Kim YH. Left ventricular function in children and adolescents with type 1 diabetes mellitus. Korean Circ J. 2010;8:125-30. DOI: https://doi.org/1 0.1111/j.1399-3038.2009.00958.x

[11] Gul K, Celebi A, Kacmaz F, Ozcan OC, Ustun I, Berker D, et al. Tissue Doppler imaging must be performed to detect early left ventricular dysfunction in patients with type 1 diabetes mellitus. Eur J Echocardiogr. 2009;10:841-6. DOI: https://doi.org/10.1093/ejechocard/jep086

[12] Shishehbor MH, Hoogwerf BJ, Schoenhagen P, Marso SP, Sun JP, Li J, et al. Relation of hemoglobin a1c to left ventricular relaxation in patients with type 1 diabetes mellitus and without overt heart disease. Am J Cardiol. 2003;91:1514-7. DOI: https://doi.org/10.1016/s0002-9149(03)00414-4

[13] Pulungan, A. Increasing incidence of DM type 1 in Indonesia. Int J Pediatr Endocrinol. 2013 (Suppl 1):O12. DOI: https://doi.org/10.1186/1687-9856-2013-S1-O12

[14] Pulungan A, Anisa D, Imada S. Diabetes Melitus Tipe-1 pada Anak : Situasi di Indonesia dan Tata Laksana. Sari Pediatri. 2019;20(6):392-400.

[15] Dabalea D, Mayer-Davis EJ, Saydah S, Imperatore G, Linder B, Divers J. Prevalence of type 1 and type 2 diabetes among children and adolescents from 2001 to 2009. JAMA. 2014;311(17):1778–86. DOI: https://doi.org/10.1001/jama.2014.3201

[16] Kim JH, Lee CG, Lee YA, Yang SW, Shin CH. Increasing incidence of type 1 diabetes among Korean children and adolescents: analysis of data from a nationwide registry in Korea. Pediatr Diabetes. 2016;17(7):519-24. DOI: https://doi.org10.1111/pedi.12324

[17] Indriyani R, Adji TH. Hubungan antara Status Kontrol Glikemik, Vitamin D dan Gizi pada Anak Diabetes Melitus Tipe 1. Jurnal Kedokteran Brawijaya. 2018:30(2):114-20. DOI: https://doi.org/10.21776/ub.jkb.2018.030.02.7

[18] Wulandari H. Korelasi antara kadar Osteocalcin, HbA1C dan 25(OH)D pada Anak dengan Diabetes Melitus Tipe 1. Jurnal Kedokteran Brawijaya. 2018;30(2):103-08. DOI: https://doi.org/10.21776/ub.jkb.2018.030.02.5

[19] Amiel SA, Sherwin RS, Simonson DC, Lauritano AA, Tamborlane WV. Impaired insulin action in puberty. A contributing factor to poor glycemic control in adolescents with diabetes. N Engl J Med. 1986;315:215–19. DOI: https://doi.org/10.1056/NEJM198607243150402

[20] Mohammad HA, Farghaly HS, Metwalley KA, Monazea EM, Hafeez HA. Predictors of glycemic control in children with type 1 diabetes mellitus in assiut-egypt. Indian J Endocrinol Metab. 2012;16(5):796–802. DOI: https://doi.org/10.4103/2230-8210.100679

[21] Paess VM, Barrett JK, Dunger DB, Gevers EF, Taylor-Robinson DC, Viner RM, et al. Factors predicting poor glycemic control in the first two years of childhood onset type 1 diabetes in a cohort from East London, UK: Analyses using mixed effects fractional polynomial models. Pediatr Diabetes. 2020; 21(2):288-99. DOI: https://doi.org/10.1111/pedi.12950

[22] Setoodeh A, Mostafavi F, Rabbani A, Hedayat T. Female sex as a risk factor for glycemic control and complications in iranian patients with type one diabetes mellitus. Iran J Pediatr. 2011;21(3):373-78.

[23] Acar CO, Epcacan S, Uner A, Ece I, Dogan M. Evaluation of left and right ventricular functions using conventional and tissue doppler echocardiography in children with type 1 diabetes mellitus. J Pediatr Endocrinol Metab. 2016;aop:1-7. DOI: https://doi.org/10.1515/jpem-2015-0453

[24] Salem M, El Behery S, Adly A, Khalil D, El-Hadidi E. Early predictors of myocardial disease in children and adolescents with type 1 diabetes mellitus. Pediatr Diabetes. 2009;10:513–21. DOI: https://doi.org/10.1111/j.1399-5448.2009.00517.x

[25] Brunvand L, Fugelseth D, Stensaeth KH, Dahl-Jørgensen K, Margeirsdottir HD. Early reduced myocardial diastolic function in children and adolescents with type 1 diabetes mellitus a population-based study. BMC Cardiovasc Disord. 2016;16:1-5. DOI: https://doi.org/10.1186/s12872-016-0288-1

[26] Gul K, Celebi A, Kacmaz F, Ozcan OC, Ustun I, Berker D, et al. Tissue Doppler imaging must be performed to detect early left ventricular dysfunction in patients with type 1 diabetes mellitus. Eur J Echocardiogr. 2009;10:841-6. DOI: https://doi.org/10.1093/ejechocard/jep086

[27] Pattoneri P, Sozzi FB, Catellani E, Piazza A, Iotti R, Michelini M, et al. Myocardial involvement during the early course of type 2 diabetes mellitus: usefulness of myocardial performance index. Cardiovasc Ultrasound. 2008;6(27):1-7. DOI: https://doi.org/10.1186/1476-7120-6-27

[28] Chadha DS, Swamy A, Malani SK, Ganjoo RK, Mathew OP. Impact of body mass index on left ventricular function. Med J Armed Forces India. 2009;65(3):203–7. DOI: https://doi.org/10.1016/S0377-1237(09)80003-8

[29] Russell-Jones D, Khan R. Insulin-associated weight gain in diabetes-causes, effects and coping strategies. Diabetes Obes Metab. 2007;9(6):799–812. DOI: https://doi.org/10.1111/j.1463-1326.2006.00686.x

[30] Lee EY, Lee Y, Jin SM, Yang HK, Jung CH, Park CY, et al. Differential association of body mass index on glycemic control in type 1 diabetes. Diabetes Metab Res Rev. 2016; 5:1-8. DOI: https://doi.org/10.1002/dmrr.2815

[31] Abd-El Aziz FM, Abdelghaffar S, Hussien EM, Fattouh AM. Evaluation of cardiac functions in children and adolescents with type 1 diabetes. J Cardiovasc Ultrasound. 207;25(1): 12–9. DOI: https://doi.org/10.4250/jcu.2017.25.1.12

[32] Despres JP, Bergeron J, Pibarot P, Mathieu P, Larose E. Abdominal obesity and the metabolic syndrome: contribution to global cardiometabolic risk. Arterioscler Thromb Vasc Biol. 2008;28:1039-49. DOI: https://doi.org/10.1161/ATVBAHA.107.159228

[33] Adal E, Koyuncu, G., Aydin, A., Celebi, A., Kavunoğlu, G., Cam, H. 2006. Asymptomatic Cardiomyopathy in Children and Adolescents with Type 1 Diabetes Mellitus: Association of Echocardiographic Indicators with Duration of Diabetes Mellitus and Metabolic Parameters. J Pediatr Endocrinol Metab, 19(5):713-726.

[34] Donaghuea KC, Marcovecchioc L, Wadwad RP, Chewe EY, Wong TY, Calliarig LE, et al. ISPAD Clinical Practice Consensus Guidelines 2018: Microvascular and macrovascular complications in children and adolescents. Pediatr Diabetes. 2018 Oct;19 Suppl 27(Suppl 27):262-74. DOI: https://doi.org/10.1111/pedi.12742