Original Article

The impact of poor glycemic control on lipid profile variables in children with type 1 diabetes mellitus

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Abstract:

BACKGROUND: Type 1 diabetes mellitus (T1DM) and its related comorbidities are considered an important health issue. This study aimed to evaluate the impact of glycemic control on lipid profile variables in children with T1DM.

MATERIALS AND METHODS: This study included 274 children ($\leq$19 years of age) with T1DM who had referred to the outpatient clinics of endocrinology in Emam-Hossein Hospital of Isfahan, Iran. Based on American Diabetes Association criteria, patients were divided into two groups including optimal glycemic control (OGC) and poor glycemic control (PGC). Mean lipid level and frequencies of lipid profile abnormalities between the two studied groups were compared.

RESULTS: Mean age of the studied population was 13 ± 5.9 years and 133 (48.5%) were boys. A total of 162 (59.1%) and 112 (40.9%) patients had PGC and OGC, respectively. Hypercholesterolemia was the most common dyslipidemia in both groups (33 [29.1%] of OGC and 63 [39.1%] of PGC patients). The frequency of high low-density lipoprotein (LDL) was significantly higher in patients with PGC than those with OCG ($P = 0.007$). The frequencies of hypercholesterolemia, hypertriglyceridemia, and low levels of high-density lipoprotein were also higher in PGC group, but did not reach the significant threshold.

CONCLUSION: It is suggested that glycemic control is in association with lipid profile abnormality in patients with T1DM. High LDL was significantly more frequent in patients with PGC than those with OGC. It is recommended to investigate the role of glycemic control on other cardiometabolic risk factors of T1DM patients. Our findings could be used for planning preventative strategies for reducing T1DM-related cardiovascular disease.

Keywords:

Children, diabetes mellitus, dyslipidemia, glycemic control, Iran

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Introduction

Type 1 diabetes mellitus (T1DM) is caused by severe insulin deficiency secondary to T-cell-mediated destruction of the insulin-producing β-cells. Data from large epidemiologic studies have demonstrated that the incidence of T1DM is increasing worldwide. It is estimated that the average annual increase in the incidence of T1DM has been 2.8% in the past decade. T1DM typically occurs in childhood and affects both glucose and lipid metabolism.[1-3]

Dyslipidemia is very common in patients with T1DM. Dyslipidemia is a significant risk factor for developing cardiovascular disease (CVD) and is associated with higher rates of mortality in patients with T1DM.[4,5] Several studies have shown that poor glycemic control (PGC) and high level of glycated hemoglobin A1c (HbA1c) in patients with T1DM are associated with

lipid peroxidation and oxidative stress, both of which contribute to atherosclerosis.[6-9] There are also evidences which demonstrated that intensive insulin therapy could have a significant positive impact on serum lipid levels and consequently on the occurrence of CVD in adulthood. Some previous studies also demonstrated that proper glycemic control could improve the lipid profile of T1DM patients.[10-12] Given the fact that CVD originated from early life and hyperlipidemia is a preventable CVD risk which is associated with glycemic control of T1DM patients, the importance of proper management of T1DM regarding achieving good glycemic control becomes more prominent.

Limited data are available on the pattern of lipid profile and its association with glycemic control in Iranian children with T1DM. In this study, we investigated the frequency of dyslipidemia and evaluated its association with glycemic control in a sample of Iranian children and adolescents with T1DM.

Materials and Methods

Study population and data source

This cross-sectional study was conducted from February 2013 to April 2014 on children with a confirmed diagnosis of T1DM who had referred to the outpatient clinics of Emam-Hossein Hospital, Isfahan, Iran. The inclusion criteria were as follows: (1) confirmed diagnosis of T1DM based on the World Health Organization guidelines[13] and (2) being lower than 19 years of age. Exclusion criteria were presence of any underlying liver, kidney, and thyroid disease and the use of medications other than insulin. Patients who were not willing or able to continue the study were also excluded from the study. After enrolling the eligible patients, the objectives and the protocol of the study were completely explained and a written informed consent was obtained from parents/caregivers. The study protocol was approved by the ethical committee of Isfahan University of Medical Sciences with a research project number of 394544. This research followed the tenets of the Declaration of Helsinki 1964.

Overall, 274 patients met the inclusion criteria and were enrolled in the study. Demographic features and clinical data of the eligible patients were collected which included age, sex, age at T1DM onset, duration of T1DM since diagnosis, weight (kg), height (cm), and body mass index (BMI, kg/m^2). After 12 h of overnight fasting, a venous blood sample was collected from each participant for measurement of HbA1c, triglyceride (TG), total cholesterol (TC), low-density lipoprotein (LDL), and high-density lipoprotein (HDL). Dyslipidemia was defined based on the American Diabetes Association (ADA) criteria[14] as having at least

one of the following: TC >170 mg/dL, HDL <40 mg/dL in men, HDL <50 mg/dL in women, LDL >100 mg/dL, and TG >150 mg/dL. Optimal glycemic control (OGC) was defined as per criteria laid by ADA guidelines[14] as follows: (1) 7.5%< HbA1c <8.5% for patients lower than 6 years of age; (2) HbA1c <8% for patients with 6–12 years of age; and (3) HbA1c <7.5% for patients with 13–19 years of age. Based on these criteria, the patients were divided into two groups including OGC and PGC. We compared the frequencies of lipid profile abnormalities in these two groups of patients.

Statistical analysis

Descriptive data are reported as mean ± standard deviation or number (percentage) as appropriate. Chi-square test and Student's *t*-test were used for comparison of categorical variables. Statistical analyses were performed using SPSS version 18 (SPSS Inc., Chicago, IL, USA) and $P < 0.05$ was considered the significant threshold. The study was approved by local ethics committee of Isfahan University of Medical Sciences (ethical code: IR. MUI. REC.1392.3.186).

Results

Of 274 eligible cases, 133 (48.5%) were boys and 141 (51.5%) were girls. The mean age was 13 ± 5.9 years (range: 6–19 years), and the mean BMI was 18.7 ± 3.8 kg/m^2. The mean age at onset of T1DM was 8.2 ± 2.6 years (range 2.5–14.5 years), and the mean duration of T1DM since diagnosis was 5.2 ± 2.7 years (range 1.0–11.0 years). Details of demographic and clinical characteristics of the study population are presented in Table 1. As shown in Figure 1, mean level of lipid profiles and Hb A1C were not significantly different between diabetic girls and boys. Table 2 presents the laboratory characteristics of the studied patients. Overall, 205 (74.8%) cases had dyslipidemia which included 96 (35.0%) patients with hypercholesterolemia, 57 (20.8%) patients with high levels of LDL, 35 (12.8%) patients with low levels of HDL, and 17 (6.2%) patients with hypertriglyceridemia.

According to the cutoffs of HbA1c recommended by the AAD,[13] 162 (59.1%) patients had PGC, whereas the remaining 112 (40.9%) had OGC. There was no significant difference in terms of age ($P = 0.8$) and gender ($P = 0.6$) between these two groups. Table 3 summarizes the frequency of different types of dyslipidemia in both groups. Hypercholesterolemia was the most common dyslipidemia in both groups, which was seen in 33 (29.1%) and 63 (39.1%) of patients with OGC and PGC, respectively. The frequency of high LDL was significantly higher in patients with PGC ($P = 0.007$). The frequencies of hypercholesterolemia, hypertriglyceridemia, and low levels of HDL were also higher in PGC group, but they did not reach the significant threshold [Table 3].

Table 1: Demographic characteristics and mean level of lipids in type 1 diabetic patients

Men level of lipids	Boys	Girls	P
Age (years)	12.8±4.2	13.3±7.1	NS
HbA1c	8.1±1.7	8.3±1.9	NS
Cholesterol (mg/dl)	80±37.4	83.2±31.9	NS
Triglyceride (mg/dl)	163.8±30.4	159.8±30.3	NS
HDL-cholesterol (mg/dl)	52.4±13.7	54.3±17.8	NS
LDL-cholesterol (mg/dl)	88.2±25.5	91.6±22.4	NS

HbA1c=Glycated hemoglobin, HDL=High-density lipoprotein, LDL=Low-density lipoprotein

Table 2: Lipid profile (mean±standard deviation) of type 1 diabetic patients with optimal glycemic control and poor glycemic control

Lipids	Patients with OGC	Patients with PGC
LDL cholesterol (mg/dl)	86.27±21.73	91.92±25.77
HDL cholesterol (mg/dl)	54.53±18.59	54.32±14.68
Cholesterol (mg/dl)	156.36±25.99	165.41±33.12
Triglyceride (mg/dl)	75.14±28.67	88.13±38.82

OGC=Optimal glycemic control, PGC=Poor glycemic control, HDL=High-density lipoprotein, LDL=Low-density lipoprotein

Table 3: Frequency (percentage) of different patterns of dyslipidemia in type 1 diabetic patients with optimal glycemic control and poor glycemic control
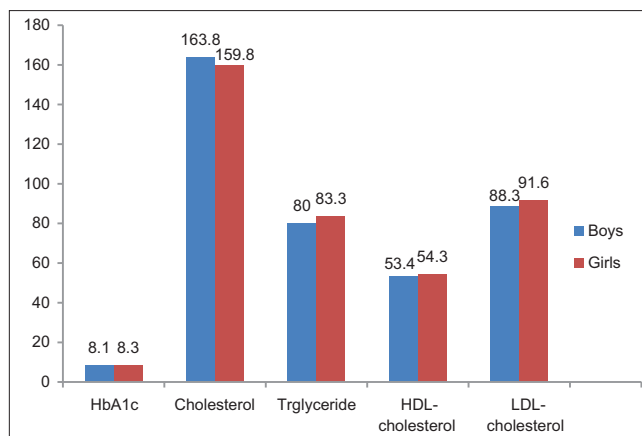
Dyslipidemia	Patients with OGC (%)	Patients with PGC (%)	P
Hypertriglyceridemia	2.7	8.4	0.057
Hypercholesterolemia	29.1	39.1	0.092
High LDL cholesterolemia	13.8	12.3	0.720
Low HDL cholesterolemia	12.8	26.6	0.007

OGC=Optimal glycemic control, PGC=Poor glycemic control, HDL=High-density lipoprotein, LDL=Low-density lipoprotein

Figure 1: Mean level of lipid profile and hemoglobin A1c in type 1 diabetic patients according to gender

Discussion

To the best of our knowledge, this study was the first report on the serum lipid profiles and glycemic control in Iranian children and adolescents with T1DM. Based on our findings, dyslipidemia was present in as high as 74.8% of Iranian children with T1DM. The most common lipid profile abnormality in our study was hypercholesterolemia (35%), which was followed by high LDL (20.8%). Furthermore, patients with PGC had a significantly higher frequency of high LDL in comparison with patients with OGC. These findings are clinically significant, as they call attention to the importance of glycemic control as a potential modifiable risk factor for dyslipidemia in T1DM.

The reported pattern of lipid profile abnormalities in T1DM varies in different studies. In line with the results of our study, Schwab *et al*.[15] reported that hypercholesterolemia was the most common lipid abnormality in 27,358 German and Austrian children with T1DM. Similarly, in a study on Korean children, Kim *et al*.[6] demonstrated that hypercholesterolemia and

high LDL were the most frequent types of dyslipidemia in T1DM. Similar findings were also found in studies by al-Naama *et al*.[16] and Rahma *et al*.[17] in Iraqi children. A recent study in Bangladesh also reported a 66% rate of hypercholesterolemia and a 75% rate of high LDL for T1DM patients.[18] It should be noted that the diabetic children in the index studies included patients with PGC as they had mean fasting blood glucose of 232.0 mg/dl and HbA1c of 9.8%. In a study on Egyptian children with T1DM, Herman *et al*.[19] and Kantoosh *et al*.[20] demonstrated that hypertriglyceridemia was the most common type of dyslipidemia. These differences across the studies are probably related to different glycemic controls across the studied populations.

Our study showed that patients with higher HbA1c level had higher frequency of high LDL. In the literature, large bodies of evidence have shown a strong association between high levels of HbA1c and an adverse lipid profile in T1DM; however, there is uncertainty about the thresholds of HbA1c beyond which lipid levels begin to change.[7,15,21,22] In a retrospective, longitudinal study on American children with T1DM, Maahs *et al*.[23] reported a positive association between HbA1c and both TC and non-HDL. In another engaging report from the SEARCH for Diabetes in Youth (SEARCH) study on American children with T1DM, Guy *et al*.[23] demonstrated that diabetic patients with HbA1c <7.5% had lower frequency of dyslipidemia, which was similar to the healthy controls. On the other hand, patients with HbA1c ≥7.5% had a significantly higher frequency of hypercholesterolemia and high LDL in comparison with healthy controls.[13] Finally, in the study of Herman *et al*.[19] on Egyptian children, high levels of HbA1c in the untreated newly diagnosed patients were associated with significantly higher serum TG level in comparison with treated patients with good glycemic control. The findings of the mentioned studies along with the results obtained from the present study highlight the important

role of glycemic control in decreasing the frequency of dyslipidemia in patients with T1DM.

Appropriate glycemic control reduces the risk of CVD and mortality in patients with T1DM. It has been shown that appropriate glycemic control over a mean of 6.5 years reduced CVD complications by 57% in T1DM.[24] Moreover, OGC is associated with fewer diabetic complications and better metabolic control.[25] At the present time, several guidelines for glycemic control exist in the literature. The ADA treatment goals for glycemic control recommend HbA1c values of lower than 7.0%.[13] The International Diabetes Federation and the American Association of Clinical Endocrinologists recommend an HbA1c value of lower than 6.5%.[26] However, only a few proportions of the patients can attain the optimal glycemic targets. As an example, only 44% of American diabetic patients have been able to maintain an HbA1c value of OGC.[27] Therefore, glycemic control remains a serious challenge for health-care systems worldwide.[28] Given the benefits of OGC, strong efforts should be taken by public health authorities and the medical community to improve glycemic control among patients with diabetes.

The findings of this study must be interpreted in view of its limitations; most importantly, the relatively small sample size. Future studies with larger sample size are warranted to further explore the pattern of dyslipidemia in different populations of Iranian children with T1DM.

It is suggested that the pattern of dyslipidemia in relation to glycemic control is varied in different populations which could be due to the genetic and ethnic lifestyle background of the populations.

Conclusion

Our study was the first report on lipid data in Iranian children with T1DM. A relatively high proportion of children with T1DM had dyslipidemia. Patients with PGC had a significantly higher frequency of high LDL in comparison with patients with OGC. More studies with larger sample size are warranted to shed light on this field. It is recommended to design longitudinal studies among T1DM patients for early detection and effective treatment of dyslipidemia, the potential modifiable risk factor of CVD, in this group of high-risk children.

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Conflicts of interest
There are no conflicts of interest.

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