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Retrospective Study

Dyslipidemia and cardiovascular disease risk factors in patients with type 1 diabetes: A single-center experience

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Abstract

BACKGROUND

Type 1 diabetes (T1D) contributes to altered lipid profiles and increases the risk of cardiovascular disease (CVD). Youth with T1D may have additional CVD risk factors within the first decade of diagnosis.

AIM

To examine risk factors for dyslipidemia in young subjects with T1D.

METHODS

Longitudinal and cross-sectional retrospective study of 170 young subjects with T1D (86 males; baseline mean age 12.2 ± 5.6 years and hemoglobin A1c 8.4% ± 1.4%) were followed in a single tertiary diabetes center for a median duration of 15 years. Predictors for outcomes of lipid profiles at last visit (total cholesterol [TC], triglycerides [TGs], low-density lipoprotein-cholesterol [LDL-c], and high-density lipoprotein-cholesterol [HDL-c]) were analyzed by stepwise linear regression models.

RESULTS

At baseline, 79.5% of the patients had at least one additional CVD risk factor (borderline dyslipidemia/dyslipidemia [37.5%], pre-hypertension/hypertension [27.6%], and overweight/obesity [16.5%]) and 41.6% had multiple (≥ 2) CVD risk factors. A positive family history of at least one CVD risk factor in a first-degree relative was reported in 54.1% of the cohort. Predictors of elevated TC: family

history of CVD (β[SE] = 23.1[8.3], *P* = 0.006); of elevated LDL-c: baseline diastolic blood pressure (DBP) (β[SE] = 11.4[4.7], *P* = 0.003) and family history of CVD (β[SE] = 20.7[6.8], *P* = 0.017); of elevated TGs: baseline DBP (β[SE] = 23.8[9.1], *P* = 0.010) and family history of CVD (β[SE] = 31.0[13.1], *P* = 0.020); and of low HDL-c levels: baseline DBP (β[SE] = 4.8[2.1], *P* = 0.022]).

CONCLUSION
Our findings suggest that elevated lipid profiles are associated with DBP and a positive family history of CVD. It is of utmost importance to prevent and control modifiable risk factors such as these, as early as childhood, given that inadequate glycemic control and elevation in blood pressure intensify the risk of dyslipidemia.

Key Words: Type 1 diabetes; Children and adolescents; Cardiovascular disease risk factors; Dyslipidemia; Hypertension; Family history of cardiovascular disease risk factors

Core Tip: Co-occurrence of type 1 diabetes (T1D) and cardiovascular disease (CVD) risk factor clustering (overweight/obesity, hypertension, family history of CVD and dyslipidemia) may contribute to early-onset CVD. Our findings demonstrated that most T1D patients already had at least one CVD risk factor during childhood, with dyslipidemia being the most prevalent. It is noteworthy that clustering of CVD risk factors was observed in approximately one-half of the cohort and that there was a positive family history of at least one CVD risk factor in more than 50% of the patients. The number and distribution of CVD risk factors were similar for males and females.

INTRODUCTION

Type 1 diabetes (T1D) is a chronic disease in children and adolescents, with a steady global increase in the number of diagnosed children[1-3]. This chronic disease is associated with well-documented, life-long increases in morbidity and mortality. Over the past several decades, there has been a marked increase in the available data on T1D, resulting in a broad understanding of many aspects of the disease including its genetics, epidemiology, and disease burden. Although a number of methods to improve clinical disease management have been assessed, wide gaps still exist in the ability to standardize clinical care and decrease disease-associated complications and burdens.

One study of the natural history of the development of atherosclerosis clearly showed a possible origin of the lesions in childhood and adolescence[4]. In recent decades, numerous studies have shown that children and adolescents with T1D exhibit subclinical cardiovascular disease (CVD) abnormalities after 10 years of disease duration[5-10]. CVD is a major complication among subjects with T1D, which may lead to a higher incidence of mortality and morbidity than found in the general population. Abnormalities in serum lipid concentrations and composition are commonly associated with both T1D and type 2 diabetes (T2D) and are believed to contribute to excess CVD risk in adults[11].

Childhood obesity and overweight have significantly increased during the last 20 years and have become a major worldwide health concern[12-15]. This trend towards increased body weight is also apparent in the T1D population[16,17] and it has recently been reported that being overweight has a significant effect on the glycemic control of

T1D patients[18]. Moreover, dyslipidemia has been documented among T1D youth aged 10-22 years, with a substantial proportion found to have lipid levels outside the recommended target range[19]. Dyslipidemia is a significant and modifiable risk factor contributing to the increased risk of atherosclerotic CVD in diabetes[20-22]. Epidemiological data on the prevalence of dyslipidemia and phenotype distribution in youth with T1D are scarce, with only limited longitudinal data on serum lipids in this population[23,24].

Co-occurrence of T1D and CVD risk factor clustering (overweight/obesity, hypertension, family history of CVD and dyslipidemia) may contribute to early-onset CVD. In this retrospective longitudinal study, we examined the association between CVD risk factors in childhood and dyslipidemia in young adulthood, and determined the prevalence of CVD risk factor clustering among T1D patients.

MATERIALS AND METHODS

Subjects

The study population included 170 young patients with T1D (86 males) followed in the National Center for Childhood Diabetes, Schneider Children's Medical Center of Israel, during the years 1998-2013. Inclusion criteria were: children/adolescents aged less than 18 years at diabetes onset, T1D diagnosis prior to 1998, and regular clinical follow-up at our diabetes center. Exclusion criteria were: Patients lost to follow-up, those with a lipid profile not available at the predetermined time points, and those with concomitant diseases likely to interfere with lipid metabolism.

The study was approved by the ethics committee of our institution, which waived the need to obtain informed consent.

Materials and methods

This longitudinal and cross-sectional retrospective cohort study was based on data collected from medical records of patients treated in our national diabetes center in accordance with the principles of Good Clinical Practice. The following data were retrieved from medical files: Sociodemographic parameters (date of birth, sex, ethnicity), anthropometric measurements (height, weight, calculated body mass index [BMI]) pubertal stage, blood pressure measurements, and diabetes-related parameters (age at diagnosis of T1D, diabetes duration, glycemic control as expressed by levels of glycosylated hemoglobin [HbA1c]), and serum lipid profile. The clinical and laboratory data were extracted from the medical files at four points in time (1998, 2003, 2008 and 2013) and a medical interview was conducted in 2017.

The routine clinical practice followed for T1D patients in our center has been quarterly clinic visits, with follow-up every 3-6 mo for weight (in light clothing using a standard calibrated scale) and height (using a commercial Harpenden-Holtain stadiometer, until adult height). BMI was calculated as weight in kilograms divided by height in meters squared. BMI-standard deviation scores (SDS) were calculated according to the recommendations of the Centers for Disease Control and Prevention[25].

The medical team (nurses and physicians) routinely questioned patients about cigarette smoking and alcohol consumption, and self-reported responses were documented in the medical files. Regular smoking was defined as smoking at least one cigarette once a week and regular alcohol consumption as drinking at least one alcoholic beverage once a week. Female patients were routinely questioned about their menstrual cycle (whether menses were absent or present and whether the cycle was regular or irregular) as well as their use of oral contraceptives.

HbA1c was routinely tested at each visit at 3-4 mo intervals. Capillary HbA1c values were measured by an automated immunochemical technique (DCA 2000; Siemens Medical Solutions Diagnostics, Tarrytown, NY, United States; 95% confidence interval [CI] 4.3%-5.7%). Our routine policy is to screen T1D patients for autoimmune thyroid disease, celiac disease, and pernicious anemia at diagnosis and annually thereafter and to screen for dyslipidemia annually. Routine screening for microvascular complications was generally initiated in pubertal patients during the first year after diagnosis, with subsequent annual assessment[26]. Screening for microvascular complications included an ophthalmologic examination, testing of urine for albumin secretion, and neurological examination (bedside Neuropathy Disability Score) to screen for distal polyneuropathy[27].

Data collection through childhood and early adulthood

BMI was calculated using the anthropometric measurements documented in the medical files. In childhood and adolescence, BMI values were converted to age- and sex-specific percentiles according to the CDC2000[25]. In adulthood, BMI values were converted according to the reference data of the National Health and Nutrition Examination Survey and National Center for Health Statistics in 2003-2006[28]. Weight status was categorized as: Obese, ≥ 95th percentile; overweight, ≥ 85th to < 95th percentiles; normal weight, ≥ 5th to < 85th percentiles and underweight, < 5th percentile[29]. Blood pressure was measured according to the recommendations of the National High Blood Pressure Education Program (NHBPEP)[30]. In childhood, percentiles for systolic blood pressure (BP) and diastolic BP were calculated according to height, sex, and age[31]. Normal BP, prehypertension, and hypertension, were defined according to the NHBPEP[30].

Total cholesterol (TC), low-density lipoprotein cholesterol (LDL-c), high-density lipoprotein cholesterol (HDL-c), and triglycerides (TGs) were converted to age- and sex-specific percentiles according to American Academy of Pediatrics (AAP) criteria for children aged 5-19 years[32]. In adults, hypercholesterolemia was defined when: TC levels were > 240 mg/dL; LDL-c levels were > 130 mg/dL; TG levels were > 150 mg/dL and HDL-c levels were < 40 mg/dL in males and < 50 mg/dL in females. CVD risk factors in T1D included: Overweight/obesity, pre-hypertension/hypertension, dyslipidemia (elevated LDL-c/elevated TG/low HDL-c) and positive family history for cardiometabolic diseases. Patients under 5 years of age were not included in the CVD risk factor analysis since lipid level reference values are less established.

Data collection in adulthood through structured interview

In accordance with IRB approval, former T1D patients no longer treated in our center were each sent a letter explaining the general goal of the study and asking permission for a detailed phone-call interview. In 2017, a structured telephone interview was carried out by a pediatric endocrinology fellow, who explained the purposes of the study, the anonymity of responses, and participants' rights. The interview contained questions pertaining to current medical status and updated family history in first-degree relatives (parents and/or siblings), as follows: (1) Habitual behavior - smoking, and if yes, age at initiation and number of cigarettes; and regular physical activity, type (aerobic/muscle-strengthening) and duration (weekly hours); (2) Autoimmune co-morbidities (thyroid disease, celiac disease, pernicious anemia), age at diagnosis; (3) Diabetes complications (retinopathy, microalbuminuria, nephropathy, neuropathy); (4) CVD risk factors (hypertension, dyslipidemia); (5) Current and past medications; (6) In females - age at menarche, regularity of menses, polycystic ovary disease, and oral contraceptive use, and if yes, indication; and (7) family history of cardio-metabolic diseases (diabetes, hypertension, dyslipidemia, CVD, and cerebrovascular episodes).

Statistical analysis

The data were analyzed using IBM SPSS statistical software (release 25.0; IBM SPSS Statistics for Windows, Armonk, NY, United States). All statistical tests were performed as two-sided. The Kolmogorov-Smirnov *z*-test was performed to test the null hypothesis that the variable has a normal distribution. Data are expressed as the mean and standard deviation (SD) for normal distribution median, interquartile range for skewed distribution, and number and percent for discrete variables. Pearson's chi-square test was used for analysis of between-group differences in discrete variables. Independent-samples *t*-tests or Mann–Whitney *U* test were used to compare between groups for continuous variables, with normal or skewed distributions, respectively. Predictors for long-term outcomes of lipid profile (TC, TGs, LDL-c, and HDL-c) were analyzed by a stepwise linear regression model. The independent variables included in all four linear model analyses were potential predictors and confounders (sex, ethnicity, Tanner stage, BMI-SDS, systolic and diastolic BP, and HbA1c levels, age at diagnosis, T1D duration, and family history of cardiometabolic diseases). $P ≤ 0.05$ was considered statistically significant.

RESULTS

The baseline characteristics of the 170 young subjects with T1D (86 males) at a mean age 12.2 ± 5.6 years are presented in Table 1. At the first evaluation, 46.5% (79) patients were prepubertal (Tanner stage 1), while 24.7% (42) were in puberty (Tanner stage 2-4) and 28.8% (49) were fully pubertal. At baseline, mean HbA1c was 8.4% ± 1.4%, 61.2%

Table 1 Baseline characteristics of the study cohort (1998)

	All, *n* = 170	Males, *n* = 86	Females, *n* = 84	*P* value
Age in yr	12.6 ± 5.6	12.4 ± 6.0	12.6 ± 5.1	0.854
Age at diabetes diagnosis	8.1 ± 4.4	8.0 ± 4.7	8.2 ± 4.1	0.735
Diabetes duration	4.4 ± 4.0	4.4 ± 4.2	4.3 ± 3.8	0.828
HbA1c, %	8.4 ± 1.4	8.6 ± 1.4	8.2 ± 1.4	0.064
HbA1c in mmol/L	68.3	70.5	66.1	
Pubertal stage, *n* (%)				
Tanner 1	79 (46.5)	47 (54.7)	32 (38.1)	0.291
Tanner 2	11 (6.5)	4 (4.7)	7 (8.3)	
Tanner 3	19 (11.2)	8 (9.3)	11 (13.1)	
Tanner 4	12 (7.1)	5 (5.8)	7 (8.3)	
Tanner 5	49 (28.8)	22 (25.6)	27 (32.1)	
Menarche		NA	48 (57.1)	
Age at menarche		NA	13.3 ± 1.3	
Ethnicity, *n* (%)				
Ashkenazi Jew	102 (60.0)	47 (54.7)	55 (65.5)	0.120
North African Jew	19 (11.2)	7 (8.1)	12 (14.3)	
Oriental Jew	19 (11.2)	10 (11.6)	9 (10.7)	
Yemenite Jew	16 (9.4)	12 (14)	4 (4.8)	
Ethiopian Jew	4 (2.4)	2 (2.3)	2 (2.4)	
Arab	10 (5.9)	8 (9.3)	2 (2.4)	
Cardiovascular disease risk factors in patients, *n* (%)				
Overweight	20 (11.8)	9 (10.5)	11 (13.1)	0.864
Obesity	8 (4.7)	4 (4.7)	4 (4.8)	
Systolic pre-hypertension, ≥ 90th to the 95th percentile	15 (8.8)	8 (9.3)	7 (8.3)	0.336
Systolic stage 1 hypertension, ≥ 95th to the < 99th percentile	19 (11.2)	12 (14)	7 (8.3)	
Systolic stage 2 hypertension, ≥ 99th percentile	8 (4.7)	5 (5.8)	3 (3.6)	
Diastolic pre-hypertension, ≥ 90th to the 95th percentile	3 (1.8)	2 (2.3)	1 (1.2)	0.670
Diastolic stage 1 hypertension, ≥ 95th to the < 99th percentile	7 (4.1)	3 (3.5)	4 (4.8)	
Diastolic stage 2 hypertension, ≥ 99th percentile	1 (0.6)	1 (1.2)	0 (0)	
Pre-hypertension, systolic and/or diastolic ≥ 90th to the 95th percentile	15 (8.8)	9 (10.5)	6 (7.1)	0.426
Stage 1 hypertension, systolic and/or diastolic ≥ 95th to the < 99th percentile	23 (13.5)	12 (14)	11 (13.1)	
Stage 2 hypertension, systolic and/or diastolic ≥ 99th percentile	9 (5.3)	6 (7)	3 (3.6)	
Lipid profile[1]	*n* = 144	*n* = 71	*n* = 73	
LDL-c, *n* (%)				0.049
< 75th percentile	63 (43.8)	27 (38)	36 (49.3)	
75th-90th percentile	47 (32.6)	21 (29.6)	26 (35.6)	

Borderline elevated 90th-95th percentile	10 (6.9)	7 (8.1)	3 (4.1)	
Elevated > 95th	24 (16.7)	16 (18.6)	8 (11)	
Triglycerides, *n* (%)				0.393
< 75th percentile	31 (21.5)	12 (16.9)	19 (26)	
75th-90th percentile	59 (41)	30 (42.3)	29 (39.7)	
Borderline elevated 90th-95th percentile	16 (11.1)	7 (9.9)	9 (12.3)	
Elevated > 95th	38 (26.3)	22 (30.9)	16 (21.9)	
HDL-c, *n* (%)				0.728
Normal level > 10th percentile	127 (88.2)	62 (87.3)	65 (89%)	
Borderline low 5th-10th percentile	9 (6.2)	4 (5.6)	5 (6.8)	
Low level < 5th percentile	8 (5.5)	5 (6.9)	3 (4.1)	
Positive family history of cardiovascular risk factors in a first-degree relative, *n* (%)				
Cardiovascular disease risk factors				
Type 2 diabetes	51 (30)	23 (26.7)	28 (33.3)	0.349
Premature coronary artery disease	24 (14.1)	10 (11.6)	14 (16.7)	0.346
Dyslipidemia	32 (18.8)	17 (19.8)	15 (17.9)	0.750
Hypertension	33 (19.4)	16 (18.6)	17 (20.2)	0.778
Cerebrovascular accident	4 (2.4)	4 (4.7)	0 (0)	0.035

Data are expressed as the number (percent) or as mean ± standard deviation. *P* values are between males and females. Highlighted in bold are significant values.

[1]Lipid profiles were available for 144 patients (71 males, 73 females). Only one female patient used statins. First-degree relatives included parents and siblings. Premature coronary artery disease (*i.e.* heart attack, treated angina, interventions for coronary artery disease, stroke, or sudden cardiac death) in male relatives < 55 years or female relatives < 65 years. HbA1c: Hemoglobin A1c; HDL-c: High-density lipoprotein cholesterol; LDL-c: Low-density lipoprotein cholesterol.

were treated by multiple daily insulin injections (the rest treated with insulin pump), and 14.1% (24/170) had co-existent autoimmune thyroid disease.

Positive family history of at least one CVD risk factor (T2D, premature coronary artery disease, dyslipidemia, hypertension or cerebrovascular accident) in a first-degree relative was reported in 54.1% (92/170) of the cohort. At baseline 128/161 patients (79.5%) already had an additional CVD risk factor in addition to the diabetes. Occurrence of multiple CVD risk factors (2 or more) was found in 67/161 patients (41.6%). The number and distribution of multiple CVD risk factors is presented in Figure 1, with no significant differences between males and females (*P* = 0.210). CVD risk factors in descending order of frequency were borderline dyslipidemia/ dyslipidemia (37.5%), pre-hypertension/hypertension (27.6%), and overweight/ obesity (16.5%), with no significant differences between males and females.

The characteristics of the study cohort at last visit at a mean age of 26.3 ± 5.7 years are presented in Table 2. Smoking was reported in 7.6% (13/170) of the cohort. 13.1% (11/84) of females reported oral contraceptive use. The number and distribution of multiple CVD risk factors at young adulthood is presented in Figure 2, with no significant differences between males and females (*P* = 0.275). CVD risk factors in descending order of frequency were borderline dyslipidemia/dyslipidemia (66.5%), overweight/obesity (39.9%), and pre-hypertension/hypertension (24.3%), with no significant differences between males and females.

Predictors for dyslipidemia are presented in Table 3. Predictors for elevated TC: Family history of CVD (β[SE] = 23.1[8.3], *P* = 0.006); elevated LDL-c: baseline diastolic blood pressure (DBP) (β[SE] = 11.4[4.7], *P* = 0.003) and family history of CVD (β[SE] = 20.7[6.8], *P* = 0.017); elevated TGs: baseline DBP (β[SE] = 23.8[9.1], *P* = 0.010) and family history of CVD (β[SE] = 31.0[13.1], *P* = 0.020); low HDL-c levels: baseline DBP (β[SE] = 4.8[2.1], *P* = 0.022).

Table 2 Characteristics of the study cohort at the last visit

	All, *n* = 170	Males, *n* = 86	Females, *n* = 84	*P* value
Age in yr	26.3 ± 5.7	26.5 ± 6.0	26.0 ± 5.5	0.540
Diabetes duration in yr	18.2 ± 5.6	18.6 ± 5.5	17.8 ± 5.8	0.375
Duration follow-up in yr	13.7 ± 3.7	14.1 ± 3.6	13.4 ± 3.9	0.222
HbA1c, %	8.0 ± 1.4	8.2 ± 1.6	7.9 ± 1.1	0.164
HbA1c in mmol/L	63.9	66.1	62.8	
Smoker, *n* (%)	13 (7.6)	7 (8.1)	6 (7.1)	0.807
Oral contraceptive use, *n* (%)			11 (13.1)	
Cardiovascular disease risk factors in patients[1]**,*n* (%)**	**All, *n* = 149**	**Males, *n* = 74**	**Females, *n* = 75**	
Diabetes only	13 (8.7)	5 (6.8)	8 (10.7)	0.578
+ 1	41 (27.5)	21 (28.4)	20 (26.7)	
+ 2	62 (41.6)	28 (37.8)	34 (45.3)	
+ 3	27 (18.1)	16 (21.6)	11 (14.7)	
+ 4	6 (4.0)	4 (5.4)	2 (2.7)	
Cardiovascular disease risk factors in patients, *n* (%)				
Overweight/obesity, *n* = 158	63/158 (39.9)	32 (40)	31 (39.7)	0.974
Hypertension, *n* = 152	37 (24.3)	26 (35.1)	11 (14.1)	**0.003**
Systolic BP > 130 mmHg	28 (18.4)	22 (29.7)	6 (7.7)	**< 0.001**
Diastolic BP > 80 mmHg	21 (13.8)	16 (21.6)	5 (6.4)	**0.007**
Dyslipidemia	113 (66.5)	57 (66.3)	56 (66.7)	0.957
LDL-c > 100 mg/dL	83 (48.8)	43 (50.0)	40 (47.6)	0.641
Triglycerides > 150 mg/dL	27 (15.9)	11 (12.7)	16 (19.0)	0.279
HDL-c < 40 mg/dL (males) and < 50 mg/dL (females)	39 (22.9)	15 (17.4)	24 (28.5)	0.099
Statin use[2]	29 (18.2)	18 (22.5)	11 (13.9)	0.316

Data are expressed as number (percent) or as mean ± standard deviation. *P* values are between males and females. Significant values are highlighted in bold.

[1]Data on cardiovascular disease risk factors were available for 149 patients (74 males, 75 females).

[2]Data on medications other than insulin (statins) were documented in the medical records of 159 patients (80 males, 79 females). BP: Blood pressure; HbA1c: Hemoglobin A1c; HDL-c; High-density lipoprotein cholesterol; LDL-c; Low-density lipoprotein cholesterol.

DISCUSSION

CVD is a leading cause of increased morbidity and mortality in subjects with T1D[33]. Co-occurrence of T1D and CVD risk factor clustering (overweight/obesity, hypertension, family history of CVD and dyslipidemia) may contribute to early-onset CVD. Goldberg *et al*[34] recently reported that clustering of cardiometabolic risk factors was more prominent in young adults diagnosed with T1D in early childhood, thus placing them at risk for premature cardiovascular morbidity and mortality. Our findings demonstrate that most T1D patients already had at least one CVD risk factor during childhood, with dyslipidemia being the most prevalent. It is noteworthy that clustering of CVD risk factors was observed in approximately one-half of the cohort and that there was a positive family history of at least one CVD risk factor in many patients. Number and distribution of CVD risk factors were similar for males and females.

Weight gain is a clinical concern in patients with T1D. The insulin resistance in overweight and obese individuals with T1D may be associated with an increased risk of vascular complications[35,36]. Over the 15-year observation period of this study, we found a marked increase in the percentage of T1D individuals with over-weight/obesity, from 16.5% to 40% of the cohort. This increase in BMI may mirror the

Table 3 Factors associated with dyslipidemia (1998-last visit)

	β (SE)	P value	95%CI
Low-density lipoprotein cholesterol			
Diastolic blood pressure 1998	11.4 (4.7)	0.003	2.0, 20.7
Positive family history of cardiovascular disease	20.7 (6.8)	0.017	7.2, 34.1
Triglycerides			
Diastolic blood pressure 1998	23.8 (9.1)	0.01	5.8, 41.8
Positive family history of cardiovascular disease	31.0 (13.1)	0.02	5.0, 57.0
High-density lipoprotein cholesterol			
Diastolic blood pressure 1998	-4.8 (2.1)	0.022	-8.9, -0.7
Total cholesterol			
Positive family history of CVD	23.1 (8.3)	0.006	6.6, 39.5

The following variables were entered into each of the four stepwise linear regression models for long-term outcomes of the lipid profile (total cholesterol, triglycerides, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol): sex, age at diagnosis, ethnicity, positive family history of type 2 diabetes, positive family history of cardiovascular disease (CVD), positive family history of dyslipidemia, positive family history of hypertension, body mass index-standard deviation scores 1998, diastolic and systolic blood pressure categories according to percentiles 1998, Tanner pubertal stage 1998, duration of diabetes 1998, and the mean HbA1c from 1998 to the last visit.
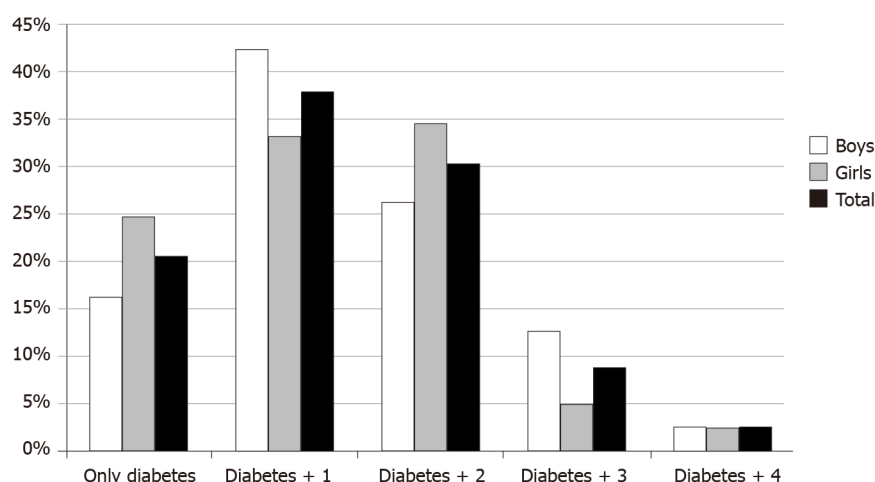

Figure 1 Number and distribution of multiple cardiovascular disease risk factors (overweight/obesity, pre-hypertension/hypertension, dyslipidemia [elevated low-density lipoprotein-cholesterol/elevated triglyceride/low high-density lipoprotein-cholesterol] and positive family history for cardiometabolic diseases) categorized by sex in childhood and adolescence. No significant differences between males and females (*P* = 0.210). Bar graphs in black represent the entire cohort, males in white, and females in gray.

increased prevalence of overweight/obesity in the general Israeli population with progression of age[37,38]. Our findings are in line with other reports from the United States, Europe, and Australia[16,39,40]. Since all T1D individuals followed in our institute receive medical nutrition therapy, the high prevalence of overweight/obesity is surprising. The excessive weight gain may perhaps be partially attributable to the intensive insulin therapy[41,42] or reflect the increase in overweight/obesity in the general Israeli population[37]. Although BMI is a good predictor of weight status, it is not a direct measure of adiposity and may slightly overestimate weight status in individuals with a relatively high muscle mass. It is therefore plausible that the rate of overweight/obesity is overestimated in our cohort. Unfortunately, body composition analysis was not available.

Hypertension is a co-morbid condition of T1D that contributes to the onset and progression of both microvascular and macrovascular complications of the disease. Studies in adults with T1D also have increased mortality rates when systolic and DBPs
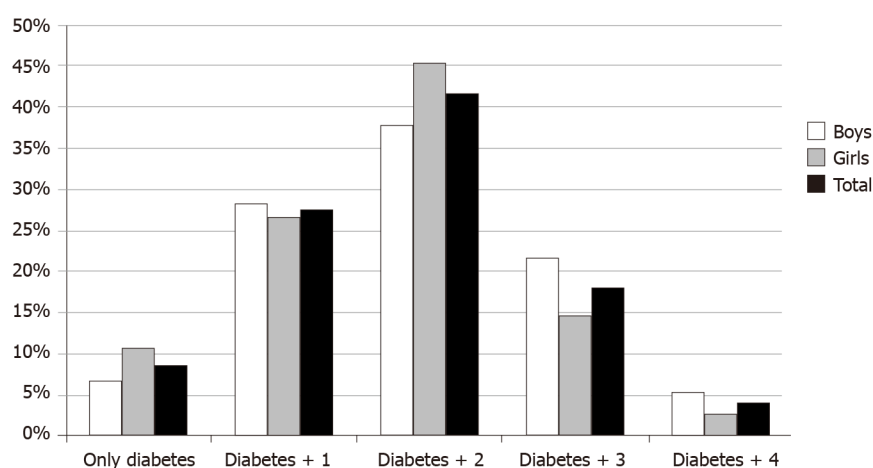
Figure 2 Number and distribution of multiple cardiovascular disease risk factors (overweight/obesity, pre-hypertension/hypertension, dyslipidemia [elevated low-density lipoprotein-cholesterol/elevated triglyceride/low high-density lipoprotein-cholesterol] and positive family history for cardiometabolic diseases) categorized by sex at young adulthood. No significant differences between males and females (P = 0.275). Bar graphs in black represent the entire cohort, males in white and females in gray.

are elevated[43,44]. Moreover, elevated BP is independently associated with an increased risk of stroke in individuals with T1D[45]. In children with T1D, the prevalence of elevated BP is reportedly as high as 4%-16%[23,46,47]. Our data show a prevalence of hypertension in approximately 25% of the cohort, both at first evaluation and at last visit, which is higher than previously reported. However, one should keep in mind that there is a known under-diagnosis of hypertension in children with T1D.

T1D and dyslipidemia are both risk factors for CVD. International guidelines recommend lifestyle modifications and then consideration of statin pharmacotherapy, depending on an individual's age and the severity of CVD risk based on LDL-c level and other risk factors[22,48,49]. Previous studies have reported a high frequency of dyslipidemia among pediatric and young adult patients with T1D[19,50,51], with a prevalence rate between 26%-72% and the highest prevalence (72%) in a Brazilian study[52]. Similarly, we found a relatively high prevalence of dyslipidemia already during childhood in slightly more than one-third of our study population, rising to about 60% at adulthood. In 2008 the American Academy of Pediatrics endorsed pharmacologic intervention for children with diabetes when LDL concentration is > 130 mg/dL[33]. Our findings suggest that, although statin therapy is recommended from the age of 8 years, physicians and patients are reluctant to initiate therapy in childhood and adolescence.

BP and cholesterol are major modifiable CVD risk factors and key components of risk prediction algorithms[53]. We found that elevated lipid levels were associated with DBP in childhood and a positive family history of CVD. An atherogenic lipid profile (specifically, elevated LDL-c in adulthood) was associated with both a positive family history of CVD and DBP in childhood; low HDL-c in adulthood was associated with DBP in childhood. In a recent report on pooled data from six large prospective United States cohort studies (of over 36000 participants), young adult exposures to elevated DBP and LDL-c were associated with incident congestive heart disease, and young adult exposure to elevated SBP and DBP was associated with incident heart failure, independent of later adult exposures[52]. These findings suggest that intervention to control modifiable risk factors during childhood, adolescence and young adulthood may reduce the future burden of CVD. Furthermore, since a family background of CVD risk factors plays such a pivotal role in the cardiometabolic health of patients, it is important to update medical files over time.

The strengths of this study lie in the fact that all the patients in our cohort received a similar standard of clinical care, as provided by the same team in a tertiary care center, and the relatively long follow-up period (median of 15 years) from childhood through adolescence to young adulthood. It should be noted that young T1D patients are referred to our center from all over the country and thus serve as a representative sample of all sectors of the Israeli population, including patients of various ethnic origins and socioeconomic status. This study had some limitations, including the single-center experience, the small sample size, and importantly, the lack of an intermediate outcome measure of CV risk/damage (*i.e.* cardiovascular risk score, intimal media thickness). Although patients were advised to perform fasting prior to

lipid profile testing, there was no guarantee that the lipid profile was taken after fasting. In the study population, there was an underrepresentation of the Arab population. Another limitation was the lack of precise data on lifestyle, including physical activity levels and dietary habits. Finally, there may be limits to the generalization of our findings, which are based on T1D patients in our country, and may differ from T1D patients in other countries. Despite these limitations, this study provides important data regarding which factors are associated with elevated CVD risk in young T1D patients.

CONCLUSION

In conclusion, our findings suggest that an elevated lipid profile is associated with DBP and positive family history of CVD. It is of utmost importance to prevent and control these types of modifiable risk factors as early as childhood, given that inadequate glycemic control and elevation in blood pressure intensify the risk for dyslipidemia. The clustering of CVD risk factors is recognized as being more prominent in patients whose TID is poorly controlled, further emphasizing the importance of rapid and intense intervention when required.

ARTICLE HIGHLIGHTS

Research background
Type 1 diabetes (T1D) contributes to altered lipid profiles and increased cardi-ovascular disease (CVD) risk.

Research motivation
Co-occurrence of T1D and CVD risk factor clustering (overweight/obesity, hypertension, family history of CVD and dyslipidemia) may contribute to early-onset CVD.

Research objectives
We examined the association between CVD risk factors in childhood and dyslipidemia in young adulthood and determined the prevalence of CVD risk factor clustering among T1D patients.

Research methods
Longitudinal and cross-sectional retrospective study of 170 young subjects with T1D followed in a single tertiary diabetes center for a median duration of 15 years.

Research results
Our findings demonstrate that most T1D patients already had at least one CVD risk factor during childhood, with dyslipidemia being the most prevalent. It is noteworthy that clustering of CVD risk factors was observed in approximately one-half of the cohort and that there was a positive family history of at least one CVD risk factor in many patients. The number and distribution of CVD risk factors were similar for males and females.

Research conclusions
Our findings suggest that an elevated lipid profile is associated with diastolic blood pressure and positive family history of CVD.

Research perspectives
It is of utmost importance to prevent and control modifiable risk factors as early as childhood, given that inadequate glycemic control and elevation in blood pressure intensify the risk for dyslipidemia.

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