ORIGINAL ARTICLE

DOI: 10.4274/jcrpe.galenos.2023.2023-12-12

J Clin Res Pediatr Endocrinol 2024;16(1):11-20

Cardiovascular Risk Factors in Adolescents with Type 1 Diabetes: Prevalence and Gender Differences

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What is already known on this topic?

Cardiovascular diseases (CVD) are the most important cause of morbidity and mortality in patients with type 1 diabetes (T1D). Children with T1D had similar or higher prevalence of being overweight (OW) or obese (Ob) compared to their healthy peers.

What this study adds?

Girls with T1D are more likely to be OW and Ob and to have CVD risk than boys. Interventions to reduce the risk of CVD in adults with T1D should begin from childhood and be tailored to compensate for gender variations.

Abstract

Objective: Cardiovascular diseases (CVD) are the most important cause of morbidity and mortality in patients with type 1 diabetes (T1D). Children with T1D have a similar or higher prevalence of being overweight (OW) or obese (Ob) compared to healthy peers. The aim of this study was to determine the prevalence of CVD risk factors in children and adolescents with T1D and the impact of obesity and sex differences on these factors.

Methods: Data of patients aged 10-21 years and who had been using intensive insulin therapy with a diagnosis of T1D for at least three years were evaluated. Patients were divided into normal weight (NW), OW and Ob groups based on body mass index percentiles. Risk factors for CVD (obesity, dyslipidemia, hypertension) were compared between groups, and impact of gender was also analyzed.

Results: Data of 365 patients (200 girls, 54.8%), were evaluated. Prevalence of OW/Ob was 25.9% and was significantly higher in girls (30.6% vs 20.1%, $p < 0.001$). Rate of hypertension was highest in OW/Ob girls followed by OW/Ob boys, and similar in NW girls and boys ($p = 0.003$). Mean low density lipoprotein cholesterol (LDL-c) and triglyceride (TG) levels were highest in OW/Ob girls, followed by OW/Ob boys, NW girls and NW boys, respectively ($p < 0.001$ and $p < 0.001$, respectively). Mean high density lipoprotein-cholesterol (HDL-c) levels were similar among groups. Rates of high LDL-c and TG were similar between OW/Ob girls and boys and higher than NW girls, followed by NW boys ($p < 0.001$ and $p < 0.001$, respectively). The rate of low HDL-c was similar in OW/Ob girls and boys, and higher than NW girls, followed by NW boys ($p < 0.001$). Overall, girls were 1.9 times more likely than boys to have two or more risk factors for CVD. Factors associated with risk for CVD in multiple logistic regression analyses were being a girl, followed by higher daily insulin dose, higher hemoglobin A1c, and longer duration of diabetes ($r = 0.856$; $p < 0.001$).

Conclusion: In spite of the increased prevalence for obesity in both sexes, the trend for CVD risk factors was greater in Ob girls, followed by Ob boys and NW girls. Girls with T1D are more likely to be OW/Ob and to have CVD risk than boys, highlighting the need for early intervention and additional studies to elucidate the causes.

Keywords: Overweight, obesity, type 1 diabetes, dyslipidemia, hypertension

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Conflict of interest: None declared
Received: 02.03.2023
Accepted: 26.07.2023

Introduction

Cardiovascular diseases (CVD) are the most important cause of morbidity and mortality in patients with type 1 diabetes (T1D) (1). CVD is more common, occurs earlier, and has a higher mortality rate in patients with T1D than individuals without diabetes (2). It has been reported that the pathogenesis of CVD accelerates in patients with T1D and although CVD rarely presents in childhood, subclinical damage to the cardiovascular system begins in the pediatric age group (3). Preventing CVD by alleviating cardiovascular risk factors is an important treatment goal for patients with T1D.

Obesity in the childhood period is also considered to be an important risk factor for CVD in adulthood (4). Being overweight (OW) and having abdominal adiposity have been associated with atherosclerosis and dyslipidemia (5). Children with T1D had similar or higher prevalence of being OW or obese (Ob) compared to their healthy peers, with rates reaching 25-35% (6-11). The risk of CVD is already high in T1D, and this risk may be increased with Ob. It is observed that Ob-related comorbidities increasingly affect individuals with T1D. Ob individuals with T1D have lower insulin sensitivity than non-Ob patients with T1D, and it has been shown recently that CVD risk factors are increased in children with T1D who are OW or Ob (12). A report of the Exchange study showed a higher prevalence of hypertension and dyslipidemia in Ob patients with T1D than in non-Ob patients (13). A recent study involving children and young adults with T1D showed a higher rate of metabolic syndrome (MS) in OW and Ob individuals (14). Unhealthy behavioral habits contribute to increased cardiovascular risk. Smoking and a sedentary lifestyle are associated with major CVD morbidity and mortality in individuals with T1D (15).

In this study we aimed to determine the prevalence of CVD risk factors in children and adolescents with T1D and the impact of OW/Ob and sex differences on these factors.

Methods

The data of patients aged 10-21 years and who had been using intensive insulin therapy (89% multiple-dose insulin therapy, 11% insulin pump) with a diagnosis of T1D for at least three years were evaluated in this descriptive, cross-sectional study. The diagnosis of T1D was confirmed by the presence of anti-GAD, anti-islet, or anti-insulin antibodies.

Body weights were measured in kilograms using a digital weighing scale (SECA, 769) with a sensitivity of 0.1 kg. Heights were measured in meters with the patients in the standing position using a stadiometer (Harpenden, Holtain Ltd., Crymych, Dyfed, UK) with a sensitivity of 0.1 cm. All the measurements were made by a nurse trained in auxology. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared and converted to BMI percentiles for age and sex using the Centers for Disease Control and Prevention (CDC) growth charts from 2000 (CDC: BMI for children and teens, http://www.cdc.gov/nccdphp/dnpa/bmi/bmi-for-age.htm). Those with a BMI <10 percentile were considered as underweight (UW), BMI ≥ 10 and BMI <85 percentile as normal weight (NW), BMI ≥ 85 and BMI <95 percentile as OW, and BMI ≥ 95 percentile as Ob. There were only two patients who were UW and we did not include the underweight group in further analysis in the study, since the number was very small and as we aimed to compare NW versus OW and Ob cases. Since the number of patients in the Ob group was low, when comparing in terms of CVD risk factors regarding genders, the OW and Ob groups were combined and the cases were divided into two groups as NW and combined OW/Ob. At the time of evaluation, the chronological age, body weight, height, BMI, blood pressure, hemoglobin A1c (HbA1c), lipid profile, and daily insulin dose per body weight (IU/kg/day) were noted. The age at diagnosis and duration of diabetes were also recorded. All cases had HbA1c values checked every three months and the HbA1c value used in the study was the average of the four HbA1c values examined in the last year before the evaluation was taken. Insulin dose was defined as the total daily units of insulin divided by the body weight in kilograms and total daily insulin dosage was obtained by randomly selecting three days from the patient records.

Blood pressure was measured with a standardized automatic sphygmomanometer in the right arm with an appropriately sized cuff in the sitting position after 10 minutes of rest, and the average of three measurements was recorded for analysis. For the definition of high blood pressure, the definitions determined by the National High Blood Pressure Education Program study group for children and adolescents were used (16). A mean systolic or diastolic blood pressure above the 95th percentile for age, sex, and height was considered high.

Lipid profiles including triglyceride (TG), total cholesterol (TC), high density lipoprotein-cholesterol (HDL-c), and low-density lipoprotein-cholesterol (LDL-c) were determined in fasting blood samples. Serum lipid levels were measured by an autoanalyzer (Roche Diagnostics). Lipid values were evaluated according to the recommendations of the American Diabetes Association and the International Diabetes Federation (17,18). LDL-c ≥ 100 mg/dL, TC ≥ 200 mg/dL, and TG ≥ 150 mg/dL were defined as high. HDL-c <40 mg/dL

for 10-16 years old and < 40 mg/dL for boys > 16 years old and < 50 mg/dL for girls > 16 years old was considered low. Dyslipidemia was considered to be an elevation of one or more lipid or lipoprotein levels, or for HDL-c, reduced levels. The presence of at least two risk factors for CVD, such as the presence of OW/Ob (BMI ≥85th percentile), high TG levels, low HDL-c levels, and hypertension were considered as increased cardiovascular risk.

The study was approved by the Hacettepe University Institutional Local Ethics Committee (approval number: 16969557-2202, date: 03.12.2019).

Statistical Analysis

Data analyses were performed using Statistical Package for the Social Sciences (SPSS) for Windows, version 22.0 (SPSS Inc., Chicago, IL, United States). The normality of the continuous variables was tested by the Kolmogrov-Smirnow test. Continuous data are described as mean ± standard deviation (SD) and categorical data were described as the number of cases (%). Statistical differences between two independent groups were compared by Student's t-test. The differences among more than two independent groups were analyzed by one-way ANOVA. When the p-value from one-way ANOVA was statistically significant, *post hoc* Bonferroni's corrections were used with either a p-value of 0.0167 or 0.0125 to know which group differ from others.

Clinical and laboratory parameters associated with having two or more risk factors for CVD were first evaluated using univariate analysis. The factors that were significant in the univariate analysis were then evaluated with multivariate logistic regression analysis. Independent variables used in the regression analysis were: gender; age at evaluation; HbA1c level; daily insulin dose; duration of diabetes; and presence of type 2 diabetes in the family. A p-value of less than 0.05 was considered statistically significant.

Results

Three hundred and sixty-five patients (200 girls, 54.8%) who were followed for at least three years with the diagnosis of T1D were included in the study. The mean age of the patients at the time of evaluation was 16.4 ± 3.7 years, and ranged from 10 to 21 years. Mean age at diagnosis was 9.6 ± 3.6 years (range 5-17 years), and mean diabetes duration was 7.0 ± 3.1 years (range 3-14 years). Most (89%) of the patients were using multiple-dose insulin therapy and 11% were using insulin pump therapy. Mean HbA1c was 8.8 ± 2.6%, and mean total daily insulin dose was 1.0 ± 0.3 IU/kg. There was no difference between boys and girls in terms of age at evaluation, HbA1c level, duration of diabetes and daily dose of insulin.

The prevalence of OW, and Ob was 19.3%, and 6.6%, respectively, in the study population (22.6%, and 8% in girls and 15.2%, and 4.9% in boys). The rate of OW and Ob was significantly higher in girls than boys (p < 0.001). The three groups (NW, OW and Ob) were at similar ages and had similar HbA1c levels at the time of the evaluation. BMI-SD score was positively correlated to the duration of diabetes (r = 0.768, p < 0.001). Daily dose of insulin per kg body weight was the highest in the Ob group, followed by the OW and NW group (1.7 ± 0.3 IU/kg/d, 1.3 ± 0.3 IU/kg/d, and 0.9 ± 0.2 IU/kg/d, respectively, p < 0.001). The Ob group had the highest rate of hypertension followed by the OW and NW groups (p < 0.001). Moreover, the Ob group had the highest mean LDL-c, TG and TC levels and the lowest HDL-c levels, followed by the OW and NW groups (p < 0.001, p < 0.001, p < 0.001 and p < 0.001, respectively) (Table 1).

Table 1. Clinical and laboratory characteristics of patients with T1D according to the BMI percentiles

	A Normal weight	B Overweight	C Obese	Overall p	A vs B p	A vs C p	B vs C p
Gender							
Girl	138 (38.0%)	45 (12.4%)	16 (4.4%)	**< 0.001**	**< 0.001***	**< 0.001***	**0.004***
Boy	131 (36.1%)	25 (6.9%)	8 (2.2%)	**< 0.001**	**< 0.001***	**< 0.001***	**0.006***
Age at evaluation (years)	16.3 ± 3.6	16.7 ± 3.4	16.7 ± 2.9	0.415			
HbA1c (%)	8.8 ± 2.5	8.7 ± 1.4	8.5 ± 1.0	0.625			
Insulin dose (IU/kg/day)	0.9 ± 0.2	1.3 ± 0.3	1.7 ± 0.3	**< 0.001**	**< 0.001***	**< 0.001***	**< 0.001***
Duration of diabetes (years)	6.4 ± 2.8	7.9 ± 2.5	10.9 ± 1.6	**< 0.001**	**0.003***	**< 0.001***	**< 0.001***
Total cholesterol (mg/dL)	168.7 ± 33.4	185.2 ± 29.5	245.6 ± 13.0	**< 0.001**	**< 0.001***	**< 0.001***	**< 0.001***
HDL-c (mg/dL)	61.7 ± 13.2	56.1 ± 8.5	47.0 ± 2.9	**< 0.001**	**0.009***	**< 0.001***	**0.003***
LDL-c (mg/dL)	99.4 ± 28.4	124.5 ± 13.0	143.8 ± 8.8	**< 0.001**	**< 0.001***	**< 0.001***	**< 0.001***
TG (mg/dL)	89.6 ± 46.5	112.3 ± 30.6	175.3 ± 12.4	**< 0.001**	**< 0.001***	**< 0.001***	**< 0.001***

*Significant after adjusting for multiple comparisons (Bonferroni's correction; p value for significance 0.0167).
HbA1c: hemoglobin A1c, HDL-c: high density lipoprotein-cholesterol, LDL-c: low density lipoprotein-cholesterol, TG: triglyceride, BMI: body mass index, T1D: type 1 diabetes

Overall, hypertension prevalence was 9.4% in the whole population. The rate of hypertension was highest in OW/Ob girls, followed by OW/Ob boys, and similar in NW girls and boys ($p = 0.003$) (Table 2). Mean LDL-c and TG levels were highest in OW/Ob girls, followed by OW/Ob boys, NW girls and NW boys, respectively ($p < 0.001$ and $p < 0.001$ respectively) (Figure 1, Panel 2, 3 and Supplementary Table 1). The mean HDL-c levels were similar among groups (Figure 1, Panel 1 and Supplementary Table 1). Rates of high LDL-c and TG were similar between OW/Ob girls and boys and higher than in NW girls, followed by NW boys ($p < 0.001$ and $p < 0.001$, respectively) (Table 2). The rate of low HDL-c was similar in OW/Ob girls and boys, and higher than in NW girls, followed by NW boys ($p < 0.001$) (Table 2). The proportion having at least two risk factors for CVD was highest in the OW/Ob girls, followed by OW/Ob boys, NW girls, and lowest in NW boys ($p < 0.001$) (Table 2). Overall, girls were 1.9 times more likely than boys to have two or more risk factors for CVD (37/199 vs 16/164).

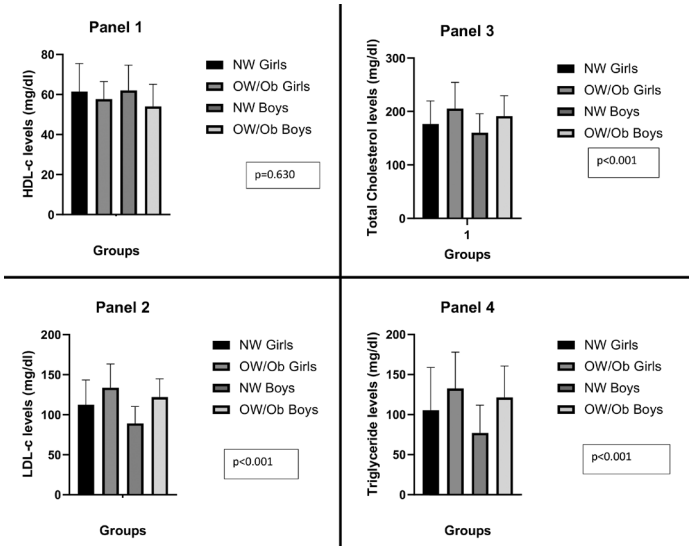

Figure 1. Lipid levels of patients with T1D according to gender and weight status. **Panel 1:** HDL-c levels: There was no significant difference among four groups. **Panel 2:** LDL-c levels: NW Girls vs OW/Ob Girls < 0.0125, NW Girls vs NW Boys < 0.0125, NW Girls vs OW/Ob Boys < 0.0125, OW/Ob Girls vs NW Boys < 0.0125, OW/Ob Girls vs OW/Ob Boys < 0.0125, NW Boys vs OW/Ob Boys < 0.0125. **Panel 3:** Total cholesterol levels: NW Girls vs OW/Ob Girls < 0.0125, NW Girls vs NW Boys < 0.0125, NW Girls vs OW/Ob Boys < 0.0125, OW/Ob Girls vs NW Boys < 0.0125, OW/Ob Girls vs OW/Ob Boys < 0.0125, NW Boys vs OW/Ob Boys < 0.0125. **Panel 4:** TG levels: NW Girls vs OW/Ob Girls < 0.0125, NW Girls vs NW Boys < 0.0125, NW Girls vs OW/Ob Boys < 0.0125, OW/Ob Girls vs NW Boys < 0.0125, OW/Ob Girls vs OW/Ob Boys < 0.0125, NW Boys vs OW/Ob Boys < 0.0125

NW: normal weight, OW: overweight, Ob: obese, HDL-c: high density lipoprotein-cholesterol, LDL-c: low density lipoprotein-cholesterol

The patients with two or more risk factors for CVD were older, had higher HbA1c levels, were using a higher dose of daily insulin per kg of body weight, and had longer duration of diabetes in comparison to those with a low risk for CVD which persisted in gender specific analyses (Table 3).

Factors associated with risk for CVD in multiple logistic regression analyses were being a girl, followed by higher daily insulin dose, higher HbA1c, and longer diabetes duration ($r = 0.856$; $p < 0.001$) (Table 4).

Discussion

The prevalence of obesity in children and adolescents with T1D is increasing, in parallel with the general population (6,19,20). One in four T1D patients in this study had a BMI over the 85th percentile, which is a higher prevalence than that of healthy Turkish children (21,22,23). Although there are no nationwide statistics on the frequency of Ob in children and adolescents with T1D, a few regional studies also found a similar prevalence (24,25). Previous research from various regions of the world revealed that 25-38.5% of children with T1D were either OW or Ob (6,8,9). According to the Diabetes Control and Complications and The Epidemiology of Diabetes Interventions and Complications Trials (EDIC), intensive insulin treatment, that is multiple insulin injections and insulin pumps, may be responsible for the increased prevalence of Ob in T1D patients compared to the non-diabetic population (26).

In the present study, girls were 1.5 times more likely to be OW/Ob than boys (30.6% vs 20.1%), whereas this is more common in boys in the non-diabetic pediatric population (21,27). There are similar studies showing that girls with T1D are particularly vulnerable to become OW/Ob, particularly during puberty (11,28). It is not known exactly why the obesity rate is higher in girls with T1D although insulin resistance, gender-specific hormonal differences, changes in body composition and energy metabolism during puberty in girls and boys may all contribute to the observed sex-related disparities in prevalence of OW/Ob in children and adolescents with T1D (14,29).

The most common cause of death in T1D is CVD. The prevalence of CVD-related and all-cause mortality is ten times higher in people with T1D than in the general population, despite recent advances in glycemic control and CVD risk management (30). The cumulative incidence of coronary artery disease by age 55 is as high as 35% in T1D compared to <10% in the non-diabetic population. Risk of stroke is four times higher in T1D compared to non-diabetic population. Similarly, people with T1D have a five-fold higher risk and incidence of peripheral vascular disease

Table 2. Clinical and laboratory characteristics of the patients with T1D according to BMI percentiles and gender

	A NW Girls (n = 38)	B OW/Ob Girls (n = 61)	C NW Boys (n = 131)	D OW/Ob Boys (n = 33)	Overall p value	A vs B p	A vs C p	A vs D p	B vs C p	B vs D p	C vs D p
Age at evaluation (yrs)	16.2 ± 2.7	16.6 ± 3.8	16.4 ± 3.7	16.9 ± 3.5	0.498						
HbA1c (%)	8.7 ± 1.6	8.5 ± 1.0	8.9 ± 3.1	8.6 ± 1.8	0.649						
Hypertension	5.8% (8/138)	21.3% (13/61)	6.1% (8/131)	15.2% (5/33)	**0.003**	**< 0.001***	**0.716**	**< 0.001***	**< 0.001***	**0.008***	**< 0.001***
TG ≥150 mg/dL	14.5% (20/138)	34.4% (21/61)	6.1% (8/131)	27.3% (9/33)	**< 0.001**	**< 0.001***	**< 0.001***	**< 0.001***	**< 0.001***	0.020	**< 0.001***
HDL-c < 40 mg/dL (girls > 16 years of age < 50 mg/dL)	11.6% (16/138)	21.3% (13/61)	6.1% (8/131)	18.2% (6/33)	**< 0.001**	**< 0.001***	**0.003***	**0.005***	**< 0.001***	0.678	**< 0.001**
LDL-c ≥100 mg/dL	36.2% (50/138)	62.3% (38/61)	22.9% (30/131)	54.6% (18/33)	**< 0.001**	**< 0.001***	**0.006***	**0.002***	**< 0.001***	0.392	**< 0.001***
Dyslipidemia	36.2% (50/138)	62.3% (38/61)	22.9% (30/131)	54.6% (18/33)		**< 0.001***	**0.006***	**0.002***	**< 0.001***	0.392	**< 0.001***
At least two criterias positivity for MS [obesity and/or TG ≥150 mg/dL and/or HDL < 40 mg/dL (girls > 16 years of age < 50 mg/dL) and/or hypertension]	11.6% (16/138)	34.4% (21/61)	5.3% (7/131)	27.3% (9/33)	**< 0.001**	**< 0.001***	**0.002***	**< 0.001***	**< 0.001***	**0.009***	**< 0.001***

*Significant after adjusting for multiple comparisons (Bonferroni's correction; p value for significance 0.0125).
yrs: years, HbA1c: hemoglobin A1c, HDL-c: high density lipoprotein-cholesterol, LDL-c: low density lipoprotein-cholesterol, TG: triglyceride, BMI: body mass index, T1D: type 1 diabetes, MS: metabolic syndrome, NW: normal weight, OW: overweight, Ob: obese

Table 3. Comparison of patients according to the presence of increased cardiovascular risk

	All patients		p	Girls		p	Boys		p
	CVD risk (+)	CVD risk (-)		CVD risk (+)	CVD risk (-)		CVD risk (+)	CVD risk (-)	
Age at evaluation (yrs)	18.2 ± 2.5	16.1 ± 2.7	**< 0.001**	18.1 ± 2.5	15.9 ± 2.3	**< 0.001**	18.6 ± 2.5	16.3 ± 3.0	**< 0.001**
Gender			**< 0.001**						
Girls	37 (69.8%)	162 (52.3%)							
Boys	16 (39.2%)	148 (47.7%)							
HbA1c (%)	9.7 ± 1.4	8.6 ± 1.9	**< 0.001**	9.5 ± 1.0	8.5 ± 1.2	**< 0.001**	10.3 ± 1.9	8.7 ± 2.4	**< 0.001**
Insulin dose (IU/kg/day)	1.4 ± 0.3	1.0 ± 0.3	**< 0.001**	1.5 ± 0.3	1.1 ± 0.2	**< 0.001**	1.3 ± 0.2	0.9 ± 0.3	**< 0.001**
Diabetes duration (yrs)	9.7 ± 1.5	6.6 ± 2.6	**< 0.001**	9.9 ± 1.9	6.6 ± 2.3	**< 0.001**	9.1 ± 2.8	6.5 ± 2.3	**< 0.001**

yrs: years, CVD: cardiovascular diseases, HbA1c: hemoglobin A1c

Table 4. Factors affecting having two or more risk factors for CVD based on multivariate regression analysis

Variables	Standardized beta coefficient	Odds ratio	95% CI		p
			Lowest	Highest	
Being a girl	5.605	11.483	6.480	18.095	**< 0.001**
Longer diabetes duration	0.832	1.137	1.033	1.573	**0.04**
Higher HbA1c	0.980	2.633	1.179	12.011	**0.03**
Higher daily insulin dose	1.036	3.409	1.695	8.714	**< 0.001**

CI: confidence interval, CVD: cardiovascular diseases, HbA1c: hemoglobin A1c

than people without diabetes. Atherosclerosis begins in childhood and is more common in children and adolescents with T1D, as shown in autopsy and epidemiological studies (31,32). Obesity may have a further impact on the risk of CVD associated with T1D. The EDIC study reported a significant increase in lipid levels and blood pressure in subjects with excessive weight gain while using intensive insulin therapy, similar to insulin resistance syndromes (26). The results of the present study showed that CVD risk factors in OW/Ob diabetic adolescents were more prevalent than that of normal-weight adolescents with T1D. We also showed that girls are more likely to have risk factors for CVD in comparison to boys in a T1D population.

Hypertension is also more common in patients with T1D than in the general population (33). Risk factors for hypertension in adolescents with T1D include obesity and hyperglycemia (34). In the current study the overall prevalence of hypertension was similar to the figures reported in previous studies (35). However, we showed that hypertension was more common in Ob girls with T1D; this is in contrast to the prevalence in the Ob non-diabetic population where hypertension is more common in boys than in girls (36,37). However, it should be noted that this difference (21% vs 15%, $p = 0.008$) was less remarkable than the difference between NW and the Ob diabetic population (5-6% vs 15-21%, $p < 0.001$).

Dyslipidemia is recognized as one of the most important CVD risk factor in patients with diabetes (38). Poor metabolic control causes diabetic dyslipidemia, which is characterized by increased LDL-c and TG levels and low HDL-c levels (39,40). The EDIC study showed that elevated LDL-c and low HDL-c lasting more than 10 years were associated with a higher CVD risk in the T1D population (41). Diabetes is a disease that causes accelerated atherosclerosis and therefore requires regular lipid monitoring and early intervention (42). Most studies showed that 26-58% of children with T1D have lipid levels above these defined values (43,44,45). Adolescent girls with T1D were reported to have higher mean TG, LDL-c, and Apolipoprotein B levels than boys, although HbA1c levels were not different from boys, suggesting that girls with T1D are at risk for CVD starting from younger ages (45). In the current study, the mean LDL-c and TG were greater in Ob girls than in Ob boys, however the prevalence of increased LDL-c and TG as CVD risk factors was similar in both Ob boys and girls with T1D and was significantly higher than that of NW girls with T1D followed by that of NW boys with T1D. In addition, similar to other studies, there was no difference in HbA1c values between the four groups. Despite comparable mean levels across all groups, prevalence of low HDL-c as a risk factor was associated with similar variation in the current study. These findings suggest that obesity plays a significant role in inducing dyslipidemia, and that female sex may also be a secondary risk factor.

A recent study showed that the rate of MS was higher in OW (8.1%) and Ob (35.3%) cases than NW (4.9%) in a population of children, adolescents and young adults with T1D (14). These rates were higher than those in the non-diabetic population where it is reported to have a median prevalence of 11.9% (range 2.8-29.3%) and 29.2% (range 10-66%) in OW and Ob children, respectively (46). The prevalence of MS (0-1%) is even lower in NW, non-diabetic children (46). In children and adolescents, a limited number of studies report a gender predilection for MS, which is mostly in favor of boys (36). However, this predilection does not seem to be preserved in patients with T1D (47,48).

The presence of at least two risk factors for CVD, such as the presence of obesity (BMI ≥85 percentile), high TG levels, low HDL-c levels, and hypertension were considered as increased cardiovascular risk in the current study. In the current study, a high proportion of OW/Ob adolescents with T1D also had other CVD risk factors including elevated TGs (31.9%), elevated blood pressure (19.1%) and low HDL-c (20.2%). Similar to our study, different studies have shown that the risk of hypertension and dyslipidemia increases with an increase in BMI and the majority of Ob children with T1D had at least two CVD risk factors (13,49). This is important because the coexistence of multiple CVD risk factors increases the risk of morbidity and mortality. Having a higher number of CVD risk factors is associated with more progressive early atherosclerotic lesions (50,51).

In the current study, approximately 20% of the girls and 10% of the boys with T1D had at least two CVD risk factors. Girls were twice as likely to have a CVD risk factor as boys. In addition to obesity, being female appears to be a risk factor in terms of CVD. In the regression analysis the most important factor increasing the CVD risk factor was being a girl. In Ob girls, the presence of CVD risk factors was approximately three times more common than in normal-weight girls and 1.3 times more common than in Ob boys (34.4% vs 11.6%, and 34.4% vs 27.3%, respectively). Brown et al. (52) showed that TC, LDL-c, BMI and blood pressure were higher in adolescent girls than boys, similar to our findings. The prevalence of co-existence of several CVD risk factors has been reported to be more common in girls than in boys (40,53,54,55).

Given the later onset of CVD in women in the general population, premenopausal women appear to be protected from CVD compared to men of similar age.

These differences among genders have been attributed to biological differences, including sex chromosomes and hormonal status, as well as to gender differences in behavioral and sociocultural aspects (56). Considering that the risk of CVD increases as estrogen levels decrease after menopause, estrogens appear to be protective against CVD. By increasing the amount of HDL-c and inhibiting LDL-c oxidation, estrogen in the blood causes a lipoprotein profile change, which reduces the accumulation of oxidized LDL-c in the arterial wall (57). Gender-related protection from CVD is lost in females with diabetes. Females with T1D have a roughly 40% greater risk of all-cause death and twice the risk of fatal and non-fatal vascular events compared to males with T1D (58). It is not fully explained why the CVD risk is higher in females with T1D compared to males. The mechanisms proposed to date argue for gender differences in both biological and psychosocial factors, as well as in the management of diabetes and CVD risk factors (35). Hormonal changes seen in women with T1D may contribute to a greater atherogenic lipid profile, insulin resistance, higher inflammation, and loss of vasoprotective effect (59). This is a mechanism that warrants further investigation. It was also thought that the higher prevalence of OW/Ob and CVD risk in adolescent girls with T1D might be related to the difficulties encountered in the management of T1D in this population. Sedentary lifestyle and physical inactivity, which are among the leading modifiable risk factors for CVD, are more common in girls with T1D compared to boys (59).

There is also substantial evidence that insulin resistance in T1D may diminish the female protection against CVD. The CACTI study has shown that adults with T1D have increased insulin resistance compared to nondiabetic controls (60) and, more recently, that this effect of T1D on insulin resistance appears to be greater in women (61). The reasons for greater insulin resistance in women with T1D compared to women without diabetes are unclear, but it is thought that differences in estrogen levels may play a role. It has been also shown that healthy girls are less insulin sensitive than boys, but compensate for their decreased sensitivity with increased insulin secretion (62). However, this compensation does not exist in diabetic children and adolescents.

It is also not clear when excess CVD risk begins in women with T1D. We have shown that sex differences in the prevalence of CVD risk factors emerge in the early course of T1D, beginning with adolescence. In particular, adolescent girls with T1D have higher CVD risk factors than boys. Therefore, early diagnosis and gender-specific intervention in girls and young women with T1D will facilitate earlier reduction of the risk of CVD with its attendant morbidity and mortality later in life.

Study Limitations

One of the strengths of this study was the large sample size of children and adolescents with a long follow-up period from a single center. Participants in the study were exposed to comparable management strategies, which is an strength. However, this study also has some limitations. First, since data were gathered retrospectively, measurements such as waist circumference were absent, despite the fact that it is optimal to evaluate obesity using waist circumference in children and adolescents. Second, some potential confounders of obesity and CVD risk, including levels of physical activity, dietary practice, and socioeconomic status, were not accounted for. Thirdly, this was not a longitudinal study, nor was it a population-based study and thus the prevalence rates are not applicable to the entire population of children and adolescents with T1D. The last limitation was that we did not compare our patients to a control group of non-diabetic children.

Conclusion

This study showed that more than a quarter of children and adolescents with T1D were OW or Ob. In spite of the increased prevalence for obesity in both sexes, the trend for CVD risk factors was increased most in Ob girls, followed by Ob boys and then girls who were of NW.

Girls with T1D are more likely to be OW and Ob and to have CVD risk factors than boys, highlighting the need for early intervention and additional studies to elucidate the causes. Interventions to reduce the risk of CVD in adults with T1D should begin from childhood and be tailored to compensate for gender variations. Individuals with T1D may experience less CVD morbidity and mortality as a result of early identification of CVD risk factors and possible gender-specific treatments, which may ultimately lead to better long-term outcomes.

Ethics

Ethics Committee Approval: The study was approved by the Hacettepe University Institutional Local Ethics Committee (approval number: 16969557-2202, date: 03.12.2019).

Informed Consent: Retrospective study.

Authorship Contributions

Surgical and Medical Practices: Doğuş Vurallı, Z. Alev Özön, E. Nazlı Gönç, Ayfer Alikaşifoğlu, Nurgün Kandemir, Concept: Doğuş Vurallı, Nurgün Kandemir, Design: Doğuş

Vurallı, E. Nazlı Gönç, Nurgün Kandemir, Data Collection or Processing: Doğuş Vurallı, Z. Alev Özön, E. Nazlı Gönç, Ayfer Alikaşifoğlu, Lala Jalilova, Analysis or Interpretation: Doğuş Vurallı, Z. Alev Özön, E. Nazlı Gönç, Ayfer Alikaşifoğlu, Nurgün Kandemir, Lala Jalilova, Literature Search: Doğuş Vurallı, Z. Alev Özön, E. Nazlı Gönç, Nurgün Kandemir, Lala Jalilova, Writing: Doğuş Vurallı, Z. Alev Özön, E. Nazlı Gönç, Ayfer Alikaşifoğlu, Nurgün Kandemir.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Rawshani A, Rawshani A, Gudbjörnsdottir S. Mortality and Cardiovascular Disease in Type 1 and Type 2 Diabetes. N Engl J Med 2017;377:300-301.
2. Soedamah-Muthu SS, Fuller JH, Mulnier HE, Raleigh VS, Lawrenson RA, Colhoun HM. High risk of cardiovascular disease in patients with type 1 diabetes in the U.K.: a cohort study using the general practice research database. Diabetes Care 2006;29:798-804.
3. Järvisalo MJ, Raitakari M, Toikka JO, Putto-Laurila A, Rontu R, Laine S, Lehtimäki T, Rönnemaa T, Viikari J, Raitakari OT. Endothelial dysfunction and increased arterial intima-media thickness in children with type 1 diabetes. Circulation 2004;109:1750-1755. Epub 2004 Mar 15
4. Park MH, Falconer C, Viner RM, Kinra S. The impact of childhood obesity on morbidity and mortality in adulthood: a systematic review. Obes Rev 2012;13:985-1000. Epub 2012 Jun 26
5. Valerio G, Iafusco D, Zucchini S, Maffeis C; Study-Group on Diabetes of Italian Society of Pediatric Endocrinology and Diabetology (ISPED). Abdominal adiposity and cardiovascular risk factors in adolescents with type 1 diabetes. Diabetes Res Clin Pract 2012;97:99-104. Epub 2012 Feb 13
6. Liu LL, Lawrence JM, Davis C, Liese AD, Pettitt DJ, Pihoker C, Dabelea D, Hamman R, Waitzfelder B, Kahn HS; SEARCH for Diabetes in Youth Study Group. Prevalence of overweight and obesity in youth with diabetes in USA: the SEARCH for Diabetes in Youth study. Pediatr Diabetes 2010;11:4-11. Epub 2009 May 15
7. Islam ST, Abraham A, Donaghue KC, Chan AK, Lloyd M, Srinivasan S, Craig ME. Plateau of adiposity in Australian children diagnosed with Type 1 diabetes: a 20-year study. Diabet Med 2014;31:686-690. Epub 2014 Mar 6
8. Baskaran C, Volkening LK, Diaz M, Laffel LM. A decade of temporal trends in overweight/obesity in youth with type 1 diabetes after the Diabetes Control and Complications Trial. Pediatr Diabetes 2015;16:263-270. Epub 2014 Jul 12
9. Fröhlich-Reiterer EE, Rosenbauer J, Bechtold-Dalla Pozza S, Hofer SE, Schober E, Holl RW; DPV-Wiss Study Group and German BMBF Competence Networks Diabetes mellitus and Obesity. Predictors of increasing BMI during the course of diabetes in children and adolescents with type 1 diabetes: data from the German/Austrian DPV multicentre survey. Arch Dis Child 2014;99:738-743. Epub 2014 May 8
10. Kapellen TM, Gausche R, Dost A, Wiegand S, Flechtner-Mors M, Keller E, Kiess W, Holl RW; DPV-Science-Initiative of the German Competence Network Diabetes and the German Competence Network Obesity (Consortium LARGE). Children and adolescents with type 1 diabetes in Germany are more overweight than healthy controls: results comparing DPV database and CrescNet database. J Pediatr Endocrinol Metab 2014;27:209-214.
11. Holl RW, Grabert M, Sorgo W, Heinze E, Debatin KM. Contributions of age, gender and insulin administration to weight gain in subjects with IDDM. Diabetologia1998;41:542-547.
12. Maahs DM, Daniels SR, de Ferranti SD, Dichek HL, Flynn J, Goldstein BI, Kelly AS, Nadeau KJ, Martyn-Nemeth P, Osganian SK, Quinn L, Shah AS, Urbina E; American Heart Association Atherosclerosis, Hypertension and Obesity in Youth Committee of the Council on Cardiovascular Disease in the Young, Council on Clinical Cardiology, Council on Cardiovascular and Stroke Nursing, Council for High Blood Pressure Research, and Council on Lifestyle and Cardiometabolic Health. Cardiovascular disease risk factors in youth with diabetes mellitus: a scientific statement from the American Heart Association. Circulation 2014;130:1532-1558. Epub 2014 Aug 28
13. Redondo MJ, Foster NC, Libman IM, Mehta SN, Hathway JM, Bethin KE, Nathan BM, Ecker MA, Shah AC, DuBose SN, Tamborlane WV, Hoffman RP, Wong JC, Maahs DM, Beck RW, DiMeglio LA. Prevalence of cardiovascular risk factors in youth with type 1 diabetes and elevated body mass index. Acta Diabetol 2016;53:271-277. Epub 2015 Jun 16
14. Pinhas-Hamiel O, Levek-Motola N, Kaidar K, Boyko V, Tisch E, Mazor-Aronovitch K, Graf-Barel C, Landau Z, Lerner-Geva L, Frumkin Ben-David R. Prevalence of overweight, obesity and metabolic syndrome components in children, adolescents and young adults with type 1 diabetes mellitus. Diabetes Metab Res Rev 2015;31:76-84.
15. Donaghue K, Jeanne Wong SL. Traditional Cardiovascular Risk Factors in Adolescents with Type 1 Diabetes Mellitus. Curr Diabetes Rev 2017;13:533-543.
16. National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents. The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. Pediatrics 2004;114(2 Suppl 4th Report):555-576.
17. American Diabetes Association. Standards of medical care in diabetes--2012. Diabetes Care 2012;35(Suppl 1):11-63.
18. Zimmet P, Alberti KG, Kaufman F, Tajima N, Silink M, Arslanian S, Wong G, Bennett P, Shaw J, Caprio S; IDF Consensus Group. The metabolic syndrome in children and adolescents - an IDF consensus report. Pediatr Diabetes 2007;8:299-306.
19. Maffeis C, Birkebaek NH, Konstantinova M, Schwandt A, Vazeou A, Casteels K, Jali S, Limbert C, Pundziute-Lycka A, Toth-Heyn P, de Beaufort C, Sumnik Z, Cherubini V, Svensson J, Pacaud D, Kanaka-Gantenbein C, Shalitin S, Bratina N, Hanas R, Alonso GT, Poran L, Pereira AL, Marigliano M; SWEET Study Group. Prevalence of underweight, overweight, and obesity in children and adolescents with type 1 diabetes: Data from the international SWEET registry. Pediatr Diabetes 2018;19:1211-1220. Epub 2018 Aug 22
20. Łuczyński W, Szypowska A, Głowińska-Olszewska B, Bossowski A. Overweight, obesity and features of metabolic syndrome in children with diabetes treated with insulin pump therapy. Eur J Pediatr 2011;170:891-898. Epub 2010 Dec 8
21. Çelmeli G, Çürek Y, Arslan Gülten Z, Yardımsever M, Koyun M, Akçurin S, Bircan İ. Remarkable Increase in the Prevalence of Overweight and Obesity Among School Age Children in Antalya, Turkey, Between 2003 and 2015. J Clin Res Pediatr Endocrinol 2019;11:76-81. Epub 2018 Sep 25
22. Deniz S, Oguzoncul AF. The prevalence of obesıty and related factors among prımary and secondary school students. Niger J Clin Pract 2019;22:1685-1692.
23. Alper Z, Ercan İ, Uncu Y. A Meta-Analysis and an Evaluation of Trends in Obesity Prevalence among Children and Adolescents in Turkey: 1990 through 2015. J Clin Res Pediatr Endocrinol 2018;10:59-67. Epub 2017 Sep 13

24. Yayıcı Köken Ö, Kara C, Can Yılmaz G, Aydın HM. Prevalence of Obesity and Metabolic Syndrome in Children with Type 1 Diabetes: A Comparative Assessment Based on Criteria Established by the International Diabetes Federation, World Health Organisation and National Cholesterol Education Program. J Clin Res Pediatr Endocrinol 2020;12:55-62. Epub 2019 Aug 22

25. Özkaya V, Eren E, Özgen Özkaya Ş, Denkboy Öngen Y. Prevalence of obesity in prepubertal and pubertal with Turkish population type 1 diabetes. Diabetol Int 2021;12:412-419.

26. Purnell JQ, Zinman B, Brunzell JD; DCCT/EDIC Research Group. The effect of excess weight gain with intensive diabetes mellitus treatment on cardiovascular disease risk factors and atherosclerosis in type 1 diabetes mellitus: results from the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study (DCCT/EDIC) study. Circulation 2013;127:180-187.

27. Lobstein T BH. Atlas of childhood obesity. World Obesity Federation, 2019.

28. Ingberg CM, Särnblad S, Palmér M, Schvarcz E, Berne C, Aman J. Body composition in adolescent girls with type 1 diabetes. Diabet Med 2003;20:1005-1011.

29. Moran A, Jacobs DR Jr, Steinberger J, Hong CP, Prineas R, Luepker R, Sinaiko AR. Insulin resistance during puberty: results from clamp studies in 357 children. Diabetes 1999;48:2039-2044.

30. Colom C, Rull A, Sanchez-Quesada JL, Pérez A. Cardiovascular Disease in Type 1 Diabetes Mellitus: Epidemiology and Management of Cardiovascular Risk. J Clin Med 2021;10:1798.

31. Järvisalo MJ, Putto-Laurila A, Jartti L, Lehtimäki T, Solakivi T, Rönnemaa T, Raitakari OT. Carotid artery intima-media thickness in children with type 1 diabetes. Diabetes 2002;51:493-498.

32. Krantz JS, Mack WJ, Hodis HN, Liu CR, Liu CH, Kaufman FR. Early onset of subclinical atherosclerosis in young persons with type 1 diabetes. J Pediatr 2004;145:452-457.

33. Ahmadizar F, Souverein P, de Boer A, Maitland-van der Zee AH. Undertreatment of hypertension and hypercholesterolaemia in children and adolescents with type 1 diabetes: long-term follow-up on time trends in the occurrence of cardiovascular disease, risk factors and medications use. Br J Clin Pharmacol 2018;84:776-785. Epub 2018 Jan 25

34. Koebnick C, Imperatore G, Jensen ET, Stafford JM, Shah AS, Mottl AK, Bell RA, Dabelea D, Liese AD, Marcovina SM, D'Agostino RB Jr, Urbina EM, Lawrence JM. Progression to hypertension in youth and young adults with type 1 or type 2 diabetes: The SEARCH for Diabetes in Youth Study. J Clin Hypertens (Greenwich) 2020;22:888-896. Epub 2020 Apr 15

35. Downie ML, Ulrich EH, Noone DG. An Update on Hypertension in Children With Type 1 Diabetes. Can J Diabetes 2018;42:199-204. Epub 2018 Mar 6

36. Barstad LH, Júlíusson PB, Johnson LK, Hertel JK, Lekhal S, Hjelmesæth J. Gender-related differences in cardiometabolic risk factors and lifestyle behaviors in treatment-seeking adolescents with severe obesity. BMC Pediatr 2018;18:61.

37. Daratha KB, Bindler RC. Effects of individual components, time, and sex on prevalence of metabolic syndrome in adolescents. Arch Pediatr Adolesc Med 2009;163:365-370.

38. Hero C, Rawshani A, Svensson AM, Franzén S, Eliasson B, Eeg-Olofsson K, Gudbjörnsdottir S. Association Between Use of Lipid-Lowering Therapy and Cardiovascular Diseases and Death in Individuals With Type 1 Diabetes. Diabetes Care 2016;39:996-1003. Epub 2016 Apr 18

39. Schofield JD, Liu Y, Rao-Balakrishna P, Malik RA, Soran H. Diabetes Dyslipidemia. Diabetes Ther 2016;7:203-219. Epub 2016 Apr 7

40. Schwab KO, Doerfer J, Marg W, Schober E, Holl RW; DPV Science Initiative and the Competence Network Diabetes mellitus. Characterization of 33 488 children and adolescents with type 1 diabetes based on the gender-specific increase of cardiovascular risk factors. Pediatr Diabetes 2010;11:357-363.

41. Orchard TJ, Forrest KY, Kuller LH, Becker DJ; Pittsburgh Epidemiology of Diabetes Complications Study. Lipid and blood pressure treatment goals for type 1 diabetes: 10-year incidence data from the Pittsburgh Epidemiology of Diabetes Complications Study. Diabetes Care 2001;24:1053-1059.

42. Glaser NS, Geller DH, Haqq A, Gitelman S, Malloy M; Lawson Wilkins Pediatric Endocrine Society Committee on Drugs and Therapeutics. Detecting and treating hyperlipidemia in children with type 1 diabetes mellitus: are standard guidelines applicable to this special population? Pediatr Diabetes 2011;12:442-459. Epub 2010 Nov 5

43. Reh CM, Mittelman SD, Wee CP, Shah AC, Kaufman FR, Wood JR. A longitudinal assessment of lipids in youth with type 1 diabetes. Pediatr Diabetes 2011;12:365-371. Epub 2011 Mar 11

44. Kershnar AK, Daniels SR, Imperatore G, Palla SL, Petitti DB, Pettitt DJ, Marcovina S, Dolan LM, Hamman RF, Liese AD, Pihoker C, Rodriguez BL. Lipid abnormalities are prevalent in youth with type 1 and type 2 diabetes: the SEARCH for Diabetes in Youth Study. J Pediatr 2006;149:314-319.

45. Macedoni M, Hovnik T, Plesnik E, Kotnik P, Bratina N, Battelino T, Groselj U. Metabolic control, ApoE genotypes, and dyslipidemia in children, adolescents and young adults with type 1 diabetes. Atherosclerosis 2018;273:53-58. Epub 2018 Apr 12

46. Al-Hamad D, Raman V. Metabolic syndrome in children and adolescents. Transl Pediatr 2017;6:397-407.

47. Harjutsalo V, Maric-Bilkan C, Forsblom C, Groop PH. Impact of sex and age at onset of diabetes on mortality from ischemic heart disease in patients with type 1 diabetes. Diabetes Care 2014;37:144-148. Epub 2013 Sep 23

48. Laing SP, Swerdlow AJ, Slater SD, Burden AC, Morris A, Waugh NR, Gatling W, Bingley PJ, Patterson CC. Mortality from heart disease in a cohort of 23,000 patients with insulin-treated diabetes. Diabetologia 2003;46:760-765. Epub 2003 May 28

49. van Vliet M, Van der Heyden JC, Diamant M, Von Rosenstiel IA, Schindhelm RK, Aanstoot HJ, Veeze HJ. Overweight is highly prevalent in children with type 1 diabetes and associates with cardiometabolic risk. J Pediatr 2010;156:923-929. Epub 2010 Mar 10

50. Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F, McQueen M, Budaj A, Pais P, Varigos J, Lisheng L; INTERHEART Study Investigators. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. Lancet 2004;364:937-952.

51. Berenson GS, Srinivasan SR, Bao W, Newman WP 3rd, Tracy RE, Wattigney WA. Association between multiple cardiovascular risk factors and atherosclerosis in children and young adults. The Bogalusa Heart Study. N Engl J Med 1998;338:1650-1656.

52. Brown TL, Maahs DM, Bishop FK, Snell-Bergeon JK, Wadwa RP. Influences of gender on cardiovascular disease risk factors in adolescents with and without type 1 diabetes. Int J Pediatr Endocrinol 2016;2016:8. Epub 2016 Apr 19

53. Schwab KO, Doerfer J, Hecker W, Grulich-Henn J, Wiemann D, Kordonouri O, Beyer P, Holl RW; DPV Initiative of the German Working Group for Pediatric Diabetology. Spectrum and prevalence of atherogenic risk factors in 27,358 children, adolescents, and young adults with type 1 diabetes: cross-sectional data from the German diabetes documentation and quality management system (DPV). Diabetes Care 2006;29:218-225.

54. Margeirsdottir HD, Larsen JR, Brunborg C, Overby NC, Dahl-Jørgensen K; Norwegian Study Group for Childhood Diabetes. High prevalence of cardiovascular risk factors in children and adolescents with type 1 diabetes: a population-based study. Diabetologia 2008;51:554-561. Epub 2008 Jan 15

55. MacKenzie KE, Wiltshire EJ, Peña AS, Gent R, Hirte C, Piotto L, Couper JJ. Hs-CRP is associated with weight, BMI, and female sex but not with endothelial function in children with type 1 diabetes. Pediatr Diabetes 2009;10:44-51. Epub 2008 Sep 15

56. EUGenMed Cardiovascular Clinical Study Group; Regitz-Zagrosek V, Oertelt-Prigione S, Prescott E, Franconi F, Gerdts E, Foryst-Ludwig A, Maas AH, Kautzky-Willer A, Knappe-Wegner D, Kintscher U, Ladwig KH, Schenck-Gustafsson K, Stangl V. Gender in cardiovascular diseases: impact on clinical manifestations, management, and outcomes. Eur Heart J 2016;37:24-34. Epub 2015 Nov 3

57. Hsu SP, Lee WS. Effects of female sex hormones on the development of atherosclerosis. Chin J Physiol 2020;63:256-262.

58. Huxley RR, Peters SA, Mishra GD, Woodward M. Risk of all-cause mortality and vascular events in women versus men with type 1 diabetes: a systematic review and meta-analysis. Lancet Diabetes Endocrinol 2015;3:198-206. Epub 2015 Feb 6

59. Smigoc Schweiger D, Battelino T, Groselj U. Sex-Related Differences in Cardiovascular Disease Risk Profile in Children and Adolescents with Type 1 Diabetes. Int J Mol Sci 2021;22:10192.

60. Schauer IE, Snell-Bergeon JK, Bergman BC, Maahs DM, Kretowski A, Eckel RH, Rewers M. Insulin resistance, defective insulin-mediated fatty acid suppression, and coronary artery calcification in subjects with and without type 1 diabetes: The CACTI study. Diabetes 2011;60:306-314. Epub 2010 Oct 26

61. Millstein RJ, Pyle LL, Bergman BC, Eckel RH, Maahs DM, Rewers MJ, Schauer IE, Snell-Bergeon JK. Sex-specific differences in insulin resistance in type 1 diabetes: The CACTI cohort. J Diabetes Complications 2018;32:418-423. Epub 2018 Jan 10

62. Hoffman RP, Vicini P, Sivitz WI, Cobelli C. Pubertal adolescent male-female differences in insulin sensitivity and glucose effectiveness determined by the one compartment minimal model. Pediatr Res 2000;48:384-388.

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