Patterns in Body Mass Index Changes in Children after Type 1 Diabetes Mellitus Diagnosis

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ABSTRACT **Background:** Pediatric patients with newly diagnosed type 1 diabetes mellitus (T1DM) are commonly treated with daily multiple insulin injections or an insulin pump. They tend to have higher body mass index-standard deviation scores (BMI-SDS) than non-diabetic children.

Objectives: To identify patterns in the changes in BMI in the 3 years after T1DM diagnosis, and to discover factors that relate to excessive weight gain.

Methods: This retrospective study included clinical and laboratory data for 194 boys and girls aged 2–18 years at the time of diagnosis and at 1, 2, and 3 years after. Their BMI values were compared to non-diabetic children using BMI percentile and z-score (standard deviation) based on the U.S. Centers for Disease Control and Prevention (CDC) growth charts.

Results: Both males and females had low mean BMI-SDS at diagnosis (-0.4499 ± 1.38743 male, 0.3050 ± 1.29887 female) that increased after 1 year (-0.0449 ± 1.14772 male, 0.1451 ± 0.98893 female). Lower glycated hemoglobin (HbA1c) at 1 year correlated with higher BMI-SDS ($r = -0.215$, $P = 0.011$). No such correlation was found in the following 2 years. The daily dose of basal insulin correlated with higher BMI-SDS at 1 year ($r = 0.183$, $P = 0.026$) and 3 years ($r = 0.297$, $P < 0.01$). No association was found between the use of an insulin pump or continuous glucose monitoring and higher BMI-SDS.

Conclusions: BMI-SDS of children with T1DM was lower than average at the time of diagnosis and rose higher than average in the 3 years following. Higher BMI-SDS was not significantly associated with sex or ethnicity. The most prominent increase happened in the first year.

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KEY WORDS: body mass index (BMI), children, obesity, type 1 diabetes mellitus (T1DM), weight gain

Type 1 diabetes mellitus (T1DM) is the most common type of diabetes mellitus in children, with an internationally increasing incidence rate [1,2]. In an autoimmune mechanism, the pancreatic beta cells are destroyed, causing insulin deficiency [3], which eventually leads to a catabolic state of the body. This reaction results in a relatively low body weight at the time of diagnosis [3,4].

Children with T1DM tend to have higher body mass index-standard deviation scores (BMI-SDS) compared to non-diabetic children, and the difference is more significant in girls [1]. Moreover, children with T1DM have a higher rate of being overweight than do non-diabetic children [5].

Children and adolescents with T1DM show a rapid increase in their BMI during the first year of treatment, while the most rapid change in weight happens in the first months of treatment, likely reflecting the amount of weight they lost before the diagnosis [6].

The weight gain is the result of the exogenous insulin's anabolic effect and of rehydration [7]. Body fat percentage is lower in untreated children with T1DM and normalizes after 6 weeks of treatment, suggesting that more fat is gained during the first months of treatment than lean body mass [4]. Recent studies show a tendency toward excessive weight gain in the first year of treatment, especially in younger children and in girls [7,8].

Overweight leads to insulin resistance even in people with T1DM, causing a significant increase in insulin doses, and challenging glycemic control [4].

Children with newly diagnosed T1DM are commonly treated with a daily regimen of multiple subcutaneous insulin injections or with an insulin pump. Previous studies have shown conflicting data on the difference between weight gain in children using insulin injections versus children using an insulin pump, and further research is needed to determine the relationship between each method and its effect on BMI changes [9].

Children with T1DM have a higher prevalence of hypertension and dyslipidemia compared with non-diabetic children [5]. Overweight and obese children are at risk for developing type 2 diabetes and cardiovascular complications [10]; therefore, it is important to investigate the changes in BMI as early as possible, starting from the diagnosis of T1DM and to examine the main factors that affect the rate and the amount of weight gain.

At the time of diagnosis, children and adolescents with T1DM have a lower BMI than non-diabetic children and adolescents of the same age; however, within a year their BMI increases and becomes higher than the BMI of non-diabetic children and adolescents of the same age and remained higher at 3 years post-diagnosis.

PATIENTS AND METHODS

This cohort study included retrospective data collection analysis. The study was approved by the Soroka University Medical Center ethics committee (study number: 0067-19-SOR).

STUDY POPULATION

We reviewed the files of all the children and adolescents with T1DM, 2–18 years of age who visited the pediatric diabetes clinic at Soroka University Medical Center. A total of 244 patients visited from the time of diagnosis until 3 year later, between the years 2008–2015. Of these children, 50 were excluded due to celiac disease and other pre-existing autoimmune conditions, premature birth, or known eating disorders. Another reason was that they stopped follow-up.

The routine clinical management for every child diagnosed with T1DM includes dietary counselling. Every child with T1DM was evaluated by a multidisciplinary team, including a professional dietician, from diagnosis followed by meetings with a dietician every 2 to 4 weeks at the initial period after diagnosis. Later, the patients were seen by a dietician every 3 months at their scheduled visits to the diabetes clinic.

COMPARISON GROUP

Each patient with T1DM was compared to his/her own measurements and to the average BMI-SDS values of non-diabetic children and adolescents, by age and sex, based on the 2000 U.S. Centers for Disease Control and Prevention (CDC) growth charts. BMI rates were analyzed at 1 year, 2 years, and 3 years after the diagnosis of T1DM.

DATA SOURCE

Data were collected from the pediatric diabetes clinic at Soroka medical hospital in Beer Sheva, Israel, and analyzed according to predetermined criteria: age, sex, insulin regimen (multiple insulin injections or an insulin pump), daily dose, glycated hemoglobin (HbA1c) levels, continuous glucose monitoring (CGM) device (yes/no), and ethnicity. The patients were divided into three age groups: young children: 2–5 years, pre-pubertal children: 6–10 for girls/ 11 for boys, and adolescents: 11–18 for girls and 12–18 for boys [Table 1].

Each child's BMI, calculated based on height and weight measurements, was compared to their own previous measurements and to non-diabetic children population, using BMI percentile and z-score (standard deviation), based on the CDC growth charts.

PROTOCOL AND STATISTICS

We compared each dependent variable to each independent dichotomous variable (for example sex), using a *t*-test for independent variables and a paired *t* -test for comparison of dependent variables with quantitative variables. To compare a dependent variable with more than two categories, we used a one-way ANOVA test with post-hoc test, and to compare two quantitative variables we used the Pearson correlation coefficient.

Statistical analysis was a 3-step analysis process:

1. **Statistical description:** We described normally distributed quantitative variables using mean and standard deviation, abnormally distributed quantitative variables using median and range, and qualitative variables by percentile distribution.
2. **Univariate analysis:** We compared dependent variables with each independent dichotomous variable (for example sex). We used a *t*-test for independent variables, and a paired *t*-test for comparison of dependent variables with quantitative variables. For comparison of a dependent variable with more than two categories, we used a one-way ANOVA test with post-hoc test. For comparison of two quantitative variables, we used the Pearson correlation coefficient. We also used an ANOVA test for repeated measurements to try and detect a trend in the changes between BMI measurements. In this step we also checked for co-linearity, confounders, and interactions.
3. **Multivariate analysis:** We built multivariate linear models for the independent variables from the previous univariate analysis that were found to be statistically and/ or clinically significant. Moreover, we tested statistically significant interactions.

Statistical analyses were performed using IBM Statistical Package for the Social Sciences statistics software, version 25 (SPSS, IBM Corp, Armonk, NY, USA) and STATA software for the statistical analysis, version 13 (StataCorp, College Station, TX, USA). $P < 0.05$ was considered statistically significant.

RESULTS

The study group comprised of all the children with newly diagnosed T1DM who visited the Soroka University Medical Center children's diabetes clinic between the years 2008–2015. A total of 194 patients met the inclusion criteria. Characteristics of the study group are presented in Table 1.

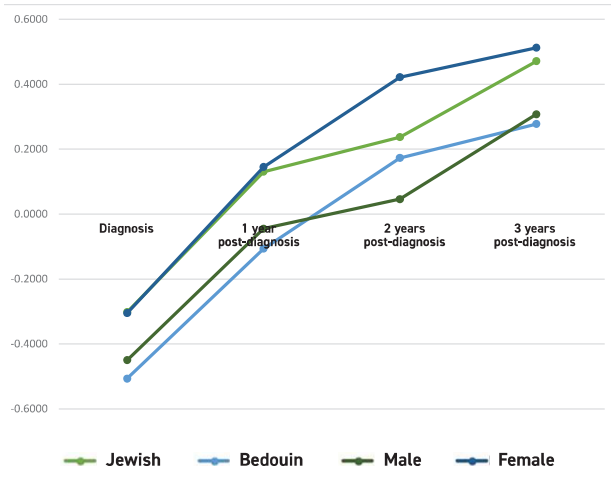
For both males and females, mean BMI-SDS was low at diagnosis (-0.4499 ± 1.38743 male, -0.3050 ± 1.29887 female) and increased after 1 year of follow-up (-0.0449 ± 1.14772 male, 0.1451 ± 0.98893 female) [Figure 1, Table 2].

No significant association was found between higher BMI-SDS and sex (*P*-value at diagnosis was 0.434, and at 3 years post-diagnosis 0.785). In the female group, the BMI-SDS values continued to increase at a much higher rate than the male group during the following year, leading to a difference of 0.38 between the female mean BMI-SDS and the male mean BMI-SDS at 2 years post-diagnosis (0.42 ± 0.925 vs. 0.046 ± 1.97), compared with a difference almost 2 times smaller 0.19 at 1 year post-diagnosis (0.15 ± 0.99 vs. -0.045 ± 1.15), and an even smaller 0.14 difference at the time of diagnosis (-0.3 ± 1.23 vs. -0.45 ± 1.39). After 3 years of follow-up, the male group mean

Table 1. Characteristics of the study population

Characteristic	Value, n (%)
Sex	
Male	107 (55.2)
Female	87 (44.8)
Ethnicity	
Jewish	119 (61.3)
Bedouin	75 (38.7)
Age category at diagnosis	
Young: 2–5 years	31 (16.0)
Pre-pubertal: 6–10 years (girls), 6–11 years (boys)	82 (42.3)
Adolescents: 11–18 years (girls), 12–18 year (boys)	81 (41.8)
Treatment regimen	
Multiple insulin injections	88 (45.4)
Insulin pump	106 (54.6)
Continuous glucose monitoring	
No	122 (62.9)
Yes	72 (37.1)

Figure 1. Mean body mass index-standard deviation scores changes by ethnicity and sex at diagnosis of type 1 diabetes mellitus and during 3 years of follow-up



BMI-SDS had increased at a rapid pace, narrowing the difference between mean male and female mean values, to 0.205 (0.51 ± 0.76 vs. 0.31 ± 0.82).

Mean BMI-SDS values for both Bedouin and Jews showed a similar trend, as the BMI-SDS values were low at the time of diagnosis and continued to increase along the 3 years of follow-up [Figure 1, Table 2].

No significant association was found between BMI-SDS and ethnicity (*P*-value at diagnosis 0.577, at 3 years post-diagnosis 0.096). In the first year of follow-up, the BMI-SDS values of the Jewish patients seemed to increase in a rapid pace very similar to that of the Bedouin patients, with a gradient of 2.31 vs. 2.5, subsequently. Nevertheless, during the second year of follow-up the mean BMI-SDS of Jewish patients was almost unchanged, with a minor difference of 0.11 (0.24 ± 1.89 at 2 years post-diagnosis vs. 0.13 ± 1.08 at 1 year post-diagnosis) while the values for the Bedouin patients continued to increase at a rapid pace, with a difference of 0.28 (0.17 ± 0.98 at 2 years vs. -0.11 ± 1.07 at 1 year post-diagnosis). In the last year of follow-up, the BMI-SDS of the Jewish patients grew faster than that of the Bedouin patients, with a difference of 0.23 (0.47 ± 0.73) at 3 years post-diagnosis compared to a difference of (0.28 ± 0.90) at 3 years post-diagnosis in the Bedouin patients.

HbA1c levels 1 year post-diagnosis of T1DM, a variable representing the level of glycemic control, had a significant negative correlation with higher BMI-SDS values at 1 year post-diagnosis (r = -0.215, $P = 0.011$) [Table 3]. However, no significant correlation was found in the following 2 years between HbA1c levels and mean BMI-SDS values.

The daily dose of basal insulin correlated significantly with the increase in BMI-SDS at 1 year (r = 0.183, $P = 0.026$) and 3 years post-diagnosis (r = 0.297, $P < 0.01$).

Last, no significant correlation was found in the 3 years of follow-up between the use of an insulin pump or a CGM and an increase in mean BMI-SDS values.

DISCUSSION

The findings of our retrospective cohort study were consistent with our hypothesis that BMI-SDS values of children with the diagnosis of T1DM are lower than average at the time of diagnosis and become higher than average in the 3 years following the diagnosis, according to the CDC BMI curves. We observed that the most significant increase happened in the first year post-diagnosis. These findings are consistent with previous studies: Newfield and colleagues [10] described that the most rapid weight gain happened within 10 weeks of diagnosis, and Manyanga et al. [3] found that most of the weight gain happened within the first 6 months.

Our study focused on the Jewish and Bedouin population in the south of Israel, which differs in its cultural and socio-demographic characteristics as well as access to health services from the Israeli population in other parts of the country. In their work on marginalized areas in Germany, Auzanneau et al. [11] found that underprivileged children had both poorer glycemic control and higher rates of overweight and obesity. In their work on overweight American youth, Clennin and co-authors [12] showed that neighborhood socioeconomic deprivation (SED) was consistently associated with overweight and obesity. In another study on childhood obesity,

Table 2. Comparison between body mass index and independent sociodemographic and clinical factors

		BMI-SDS at diagnosis			BMI-SDS 1-year post-diagnosis			BMI-SDS 2 years post-diagnosis			BMI-SDS 3 years post-diagnosis		
		N	Mean	*P*-value	N	Mean	*P*-value	N	Mean	*P*-value	N	Mean	*P*-value
Sex	Male	91	-0.4499 ± 1.38743	0.434	88	-0.0449 ± 1.14772	0.342	84	0.04583 ± 1.969088	0.240	81	0.3075 ± 0.82103	0.785
	Female	78	-0.3050 ± 1.29887		69	0.1451 ± 0.98893		67	0.42164 ± 0.925017		68	0.5125 ± 0.76294	
Ethnicity	Jewish	102	-0.3017 ± 1.35835	0.577	96	0.1307 ± 1.08245	0.846	93	0.23699 ± 1.889658	0.525	95	0.4713 ± 0.72845	0.096
	Bedouin	67	-0.50687 ± 1.32559		61	-0.106393 ± 1.07308		58	0.1734 ± 0.981364		54	0.27759 ± 0.90395	
DKA at diagnosis	Yes	64	-0.55141 ± 1.36338	0.5873	56	0.0960714 ± 1.09747	0.7162	55	0.0251 ± 2.278686	0.2552	59	0.4022 ± 0.76149	0.6827
	No	104	0.30558 ± 1.31117		100	-0.0167 ± 1.05611		95	0.2994 ± 1.011847		89	0.38034 ± 0.80935	
CGM	Yes	60	-0.44133 ± 1.4155	0.4254	63	0.0885714 ± 1.18494	0.4742	61	0.0895 ± 2.191043	0.2006	85	0.36741 ± 0.78307	0.2734
	No	109	-0.35092 ± 1.31058		94	0.0051064 ± 1.01167		90	0.296 ± 1.027506		64	0.44578 ± 0.82373	
DKA events*	Yes	25	-0.0284 ± 1.30811	0.7289	26	-0.098077 ± 1.23091	0.5245	24	0.2425 ± 0.976655	0.4055	22	0.53273 ± 0.5526	0.058
	No	144	-0.44458 ± 1.34652		131	0.0657252 ± 1.05261		127	0.2069 ± 1.694036		127	0.37827 ± 0.8339	

BMI-SDS = body mass index-standard deviation scores, CGM = continuous glucose monitoring, DKA = diabetic ketoacidosis
*DKA events in 3 years post-diagnosis of type 1 diabetes mellitus

Kassem and colleagues [13] found that in the Arab population that lives in villages and rural areas in the north-east area of Israel, pre-pubertal girls were at high a risk for developing obesity. Therefore, our results, demonstrating a higher mean BMI-SDS in the Jewish population compared with the Bedouin population in every year since the diagnosis, were unexpected, although they did not reach a statistically significant difference. A larger sample may be needed for future research to achieve significant differences. Yet, similar to our findings, de Vries et al. [5] showed no statistically significant association with ethnicity in their study group of Jewish and Arab children in Israel.

Mean BMI-SDS values were higher in females through the entire 3-year follow-up period, yet no significant association between BMI-SDS and sex was found. Łuczyński and co-authors [1] found that girls gained more weight than boys; however, in a study by Davis and associates [4], the girls were thinner at diagnosis and at 1 year post-diagnosis.

In the first year following the diagnosis, where the greatest increase in BMI-SDS occurred, a significant correlation was found between high BMI-SDS values and low HbA1c values, corresponding with the findings of de Vries et al. [5] and Nansel and colleagues [9]. In another study, Tittel and co-authors [14] found a significant correlation between lower BMI-SDS and diabetic ketoacidosis (DKA) events, which was not found in our study. Both HbA1c and DKA events are parameters indicating the level of glycemic control, yet DKA events are extreme outcomes of poor glycemic control, reflecting dramatic shifts of blood sugar levels; therefore, it is plausible that only HbA1c could be linked to BMI-SDS increase in our study group.

The daily dose of basal insulin was significantly associated with the increase in BMI-SDS at both 1 year and 3 years post-diagnosis, this discovery corresponds with the findings of Nansel et al. [9] and may be explained by the anabolic effect of insulin, and/or by the change in eating habits following the treatment, as suggested by de Vries and associates [5]. Unfortunately, we could not retrieve an accurate estimation of the average total daily insulin dosage and the duration of the honeymoon period. It should be noted that the duration honeymoon period has an important impact on total daily insulin dosage and on the time of transition to insulin pump usage.

Our findings showed no significant relation between the use of insulin pump treatment and BMI-SDS values, corresponding with previous studies by Łuczyński and colleagues [1], who found the same rates of overweight and obesity in children with insulin pumps and those using multiple insulin injections. In contrast, de Vries et al. [5], found an association between the use of an insulin pump and lower BMI-SDS. Nansel and co-authors [9] found the same association only in their treatment group that consisted of children who received family-based behavioral intervention to improve diabetes management.

Table 3. Correlations between body mass index SD scores (BMI-SDS) and clinical factors over 3 years since diagnosis of type 1 diabetes mellitus

		HbA1c at diagnosis	HbA1c 1 year post-diagnosis	HbA1c 2 years post-diagnosis	HbA1c 3 years post-diagnosis	Continuous glucose monitoring	DKA events in 3 years post-diagnosis (yes=1, no=0)	Daily dose (basal insulin units) 1 year post-diagnosis	Daily dose (basal insulin units) 2 years post-diagnosis	Daily dose (basal insulin units) 3 years post-diagnosis	Use of insulin pump (% of all 3 years)
BMI-SDS at diagnosis	Pearson Correlation	-0.160	-0.134	0.011	0.088	-0.032	0.110	0.304**	0.357**	0.341**	0.035919
	Sig (2 tailed)	0.056	0.115	0.901	0.309	0.677	0.154	0.000	0.000	0.000	0.643
	N	144	139	135	137	169	169	152	146	135	169
BMI-SDS, 1 year post-diagnosis	Pearson correlation	-0.030	-.215*	-0.157	0.020	0.038	-0.056	.183*	.176*	0.133	0.052
	Sig (2 tailed)	0.735	0.011	0.070	0.821	0.637	0.482	0.026	0.036	0.131	0.518
	N	132	138	133	131	157	157	148	141	131	157
BMI-SDS 2 years post-diagnosis	Pearson correlation	-0.014	-0.055	-0.033	0.074	-0.064	0.008	0.111	0.096	0.020	-0.012
	Sig (2 tailed)	0.879	0.532	0.707	0.405	0.438	0.921	0.197	0.255	0.822	0.885
	N	130	129	135	129	151	151	137	141	127	151
BMI-SDS, 3 years post-diagnosis	Pearson correlation	-0.039	-0.151	-0.128	-0.066	0.049	0.069	0.240**	0.288**	0.297**	0.004012
	Sig (2 tailed)	0.664	0.087	0.149	0.439	0.555	0.404	0.004	0.001	0.000	0.961
	N	127	129	129	138	149	149	139	136	141	149

*Correlation is significant at the 0.05 level (2-tailed)
**Correlation is significant at the 0.01 level (2-tailed)
BMI-SDS = body mass index-standard deviation scores, DKA = diabetic ketoacidosis, HbA1c = glycated hemoglobin

STRENGTHS

This study included a long follow-up period and a large amount of data collected from a pediatric diabetes clinic of a large tertiary center, treating children from the early age of 2 years to 18 years, from both Jewish and Bedouin ethnicities.

LIMITATIONS

Our study focused on children from the south of Israel, with its unique socio-demographic and geographic characteristics. Caution is advised in generalizing our experience to the entire Israeli pediatric population or to other populations worldwide. Further research on children from different ethnicities living in other areas of Israel should be considered to examine the impact of environmental factors or diseases like T1DM on children's weight gain. Although CDC growth charts are a commonly used tool in pediatric research, as used for example by Nansel et al. [9] and by de Vries et al. [5], it was recently found in a study on 15,000 Israeli children [15] that in both girls and boys, the average BMI values were higher than in the 2000 CDC BMI curves and the WHO curves constructed in 2006, which are used by Israel Ministry of Health. Further research may require a comparison of an updated anthropometric measurements of children in the south of Israel, to children from other areas of the country, as suggested previously. Should the pediatric research community create new growth charts based on current BMI data that are higher due to the obesity epidemic, or should we continue to use the current CDC or WHO measures? We believe that as we aspire to help children reach healthier BMI, using the current charts is more appropriate.

Use of additional biochemical markers and anthropometric measurements, such as lipid profile and waist to height ratio, as described in the work of Al-Hamad and colleagues [16], may be considered to assess the children's adiposity.

In this study, no data were collected on patient diets, their level of exercise, and their sleeping habits, due to its being a retrospective study. Prospective study is needed to collect the data and examine their influence on the children's weight gain.

CONCLUSIONS

BMI-SDS of children with T1DM was lower than average at the time of diagnosis and rose higher than average in the 3 years following. Higher BMI-SDS was not significantly associated with sex or ethnicity. The most prominent increase happened in the first year.

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Capsule

Germinal centers need some TSLP

Thymic stromal lymphopoietin (TSLP) promotes allergic responses within barrier tissues and is a target for therapeutic inhibition in severe asthma. The contributions of signaling through the TSLP receptor on B and T cells to germinal center (GC) antibody responses are poorly understood. **Domeier** and colleagues used mouse models lacking TSLP or its receptor to investigate how loss of TSLP signaling impairs antibody formation in GCs. Conditional deletion of the TSLP receptor in T cells impaired differentiation of T follicular helper cells that support GC B cells. However, conditional deletion of the TSLP receptor in B cells augmented antigen-specific GCs and memory B cells. TSLP is thus a key cytokine used by both B and T cells to achieve optimal GC function.

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Capsule

A different antibody angle in malaria

Natural killer (NK) cells have been shown to mediate immune responses against the malaria parasite *Plasmodium falciparum* using multiple effector functions. **Odera** et al. showed that *P. falciparum* merozoites marked by antibodies can induce NK cell degranulation and interferon-γ production. This response was not strain specific and reduced invasion of merozoites into uninfected red blood cells. Using a controlled human malaria infection study in adults, the authors observed that antibody-dependent NK (ab-NK) cell activity correlated directly with the control of parasitemia. In addition, in a cohort of children living in an endemic malaria setting, ab-NK cell frequency increased with age, was boosted during *P. falciparum* infection, and was linked to a reduced risk of clinical malaria. These findings highlight a key role for antibody-mediated NK cell responses during malaria.

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