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Preservation of C-Peptide Levels in Children with New-Onset Type 1 Diabetes: A Comparison Based on Body Mass Index

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ABSTRACT

Aim: The contemporaneous increase in type 1 diabetes (T1D) and obesity prevalence in children has led to conflicting reports regarding the effects of weight excess on beta-cell function and clinical manifestation of T1D. We aimed to analyze the association between body mass index (BMI) and beta-cell function in a large cohort of new-onset T1D youth.

Material and Methods: This study included 204 consecutive children with T1D aged 1-18 years. We retrospectively reviewed the medical data. The preservation of C-peptide was defined as a C-peptide level ≥0.6 ng/mL. Comparisons of variables between groups were made using appropriate statistical procedures.

Results: Eighteen percent of children were overweight or obese. Overweight/obesity was associated with significantly higher C-peptide levels at onset [0.57 (0.05-2.99) vs 0.41 (0.05-2.58) ng/ml, p=0.01]. Preservation of C-peptide levels was observed in 67% of patients. Patients with preserved C-peptide levels were older at onset [10.4 (1.9-16.5) vs 7.5 (1.1-17.3) yr, p<0.001], more likely to be pubertal (61.2% vs 22.6%, p<0.001) and had a higher BMI SDS (0.03±1.37 vs -0.67±1.47, p=0.001). The proportion of individuals with preserved C-peptide levels increased with increasing BMI, but the difference did not reach statistical significance (29.9% to 45.9%, p=0.06). While there was a positive correlation between BMI SDS and C-peptide levels (rs=0.24, p=0.001), HbA1c levels negatively correlated with BMI SDS (r=-0.16, p=0.025).

Conclusion: Overweight/obesity was present in a significant proportion of the study population. Obese and overweight children had a greater residual beta-cell function at the onset of T1D. It could be speculated that they were diagnosed at an earlier phase of beta-cell damage.

Keywords: *Type 1 diabetes, Obesity, Overweight, C-peptide, Children*

Yeni Tanı Tip 1 Diyabetli Çocuklarda Korunmuş C-Peptid Düzeyleri: Vücut Kütle İndeksine Dayalı Bir Karşılaştırma

ÖZ

Amaç: Çocuklarda tip 1 diyabet (T1D) ve obezite prevalansındaki eşzamanlı artış, aşırı kilonun beta hücre fonksiyonu ve T1D'nin ortaya çıkışı üzerine etkilerine dair çelişkili raporlara yol açmıştır. Yeni tanı T1D'li çocuklardan oluşan geniş bir kohortta vücut kütle indeksi (VKİ) ile beta hücre fonksiyonu arasındaki ilişkiyi incelemeyi amaçladık.

Gereç ve Yöntemler: Bu çalışmaya 1-18 yaş arası T1D tanılı 204 ardışık çocuk dahil edildi. Tıbbi verileri geriye dönük olarak inceledik. Korunmuş C-peptid düzeyi ≥0.6 ng/mL olarak tanımlandı. Değişkenlerin gruplar arası karşılaştırmaları uygun istatistiksel prosedürler kullanılarak yapıldı.

Bulgular: Çocukların %18'i aşırı kilolu veya obezdi. Fazla kilo/obezite, tanı anında önemli ölçüde daha yüksek C-peptid seviyeleri ile ilişkiliydi [0.57 (0.05-2.99)'ye karşı 0.41 (0.05-2.58) ng/ml, p=0.01]. Hastaların %67'sinde C-peptid düzeylerinin korunduğu gözlendi.

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Korunmuş C-peptid düzeyi grubundaki hastalar tanı anında daha ileri yaştaydı [10.4 (1.9-16.5)'e karşı 7.5 (1.1-17.3) yıl, p<0.001], pubertal olma olasılıkları daha yüksekti (%61.2'ye karşı %22.6, p<0.001) ve daha yüksek VKİ SDS'e sahipti. (0.03±1.37 vs -0.67±1.47, p=0.001). Korunmuş C-peptid seviyelerine sahip olguların oranı, artan VKİ ile artmaktaydı ancak fark istatistiksel anlamlılığa ulaşmadı (%29.9 ila %45.9, p=0.06). VKİ SDS ile C-peptid seviyeleri arasında pozitif korelasyon varken (rs=0.24, p=0.001) HbA1c seviyeleri VKİ SDS ile negatif korelasyon gösterdi (r=-0.16, p=0.025).

Sonuç: Fazla kilo/obezite, çalışma popülasyonunun önemli bir kısmında mevcuttu. Obez ve fazla kilolu çocuklar, T1D başlangıcında daha fazla rezidüel beta hücre fonksiyonuna sahipti. Bu çocukların beta hücre hasarının daha erken bir aşamasında tanı aldıkları söylenebilir.

Anahtar Sözcükler: *Tip 1 diyabet, Obezite, Fazla kilo, C-peptid, Çocuk*

INTRODUCTION

Although type 1 diabetes (T1D) is defined by a lack of insulin, the progression rate of beta-cell loss varies greatly among patients. Some individuals exhibit residual beta-cell function at diagnosis, and a significant proportion of children with newly diagnosed diabetes may have a clinically important residual beta-cell reserve (1). The preservation of residual beta-cell function, measured by C-peptide level, has a protective effect on diabetes complications (2, 3). The Diabetes Control and Complications Trial (DCCT) showed that a stimulated C-peptide value ≥0.6 ng/mL was associated with less retinopathy, nephropathy, and hypoglycemia (4).

Determining the frequency of residual beta-cell reserve in children with T1D has important clinical implications. Many clinicians use the C-peptide level to classify patients as having T1D or type 2 diabetes in addition to other findings such as the presence of diabetes-related autoantibodies. Most patients with T1D are relatively insulin-deficient after diagnosis compared to those with type 2 diabetes (5). However, the classification of diabetes may be challenging in some cases due to the overlap of clinical and laboratory findings among types. Additionally, initial C-peptide levels may help predict beta-cell function failure at the disease course (6).

Paralleling the increasing worldwide prevalence of obesity and type 2 diabetes in youth, the prevalence of overweight in children at the time of T1D diagnosis has also increased strikingly (7). Studies that focused on the association of body mass index (BMI) on beta-cell function in T1D report conflicting data. Some studies found that heavier children and adolescents with T1D had higher C-peptide levels at diagnosis and follow-up (8). On the other hand, it is suggested that weight excess might reflect insulin resistance with the overload of beta-cell and eventually accelerate T1D onset, contributing to its increased incidence (9).

This analysis of a large, new-onset pediatric T1D population evaluates the relationship between C-peptide levels and BMI. In addition, we aimed to address whether age influences this association.

MATERIAL and METHODS

The medical records of patients aged 1–18 years with T1D followed-up at Karadeniz Technical University Hospital between 2006 and 2021 were reviewed retrospectively. Age, BMI, pubertal status, HbA1c, pH, postprandial C-peptide level, T1D-associated antibodies including glutamic acid decarboxylase (GADA; detection limit <1.0 U/mL), islet cell (ICA; detection limit <2.0 U/mL), and anti-insulin (AIA; detection limit <2.0 U/mL) were examined at T1D onset. According to their BMI, patients were categorized as overweight/obese (Overweight: 85th to 95th percentile and obese: ≥95th percentile) and non-overweight/obese (lean) groups. BMI standard deviation scores (SDSs) were calculated according to Turkish child growth reference data using an online calculator program (http://www.childmetrics.org) (10). C-peptide levels were estimated by electrochemiluminescence (ECLIA) and determined to a sensitivity of 0.1 ng/mL. HbA1c was measured by spectrophotometric method, and the presence of AIA, ICA, and GADA was determined by chemiluminescence immunoassay (CLIA). T1D was diagnosed according to the International Society for Pediatric and Adolescent Diabetes guidelines, based on symptoms of insulin deficiency, elevated blood glucose and HbA1c, and a lack of family history of genetic diabetes (11). Diabetic ketoacidosis (DKA) at diagnosis was determined as blood glucose >200 mg/dL, venous pH <7.3 or bicarbonate <15 mmol/, and presence of ketonemia or ketonuria (12). The preservation of C-peptide, indicating residual beta-cell function, was defined as a stimulated C-peptide level ≥0.6 ng/mL associated with clinical significance in the DCCT (13). As C peptide was measured two hours after meal consumption, it was considered stimulated (after restoring metabolic status, on average 2-3 days after diagnosis). C-peptide values in the undetectable range were assigned a value of 0.05 ng/ml (half of the lower limit of detection) for the analyses. We compared the characteristics between overweight/obese and non-overweight/obese groups and those with and without preserved beta-cell function. Patients were further

stratified into subgroups according to age, pubertal status, autoantibody presence, and DKA status.

IBM SPSS Statistics for Windows, version 24 (IBM Corp., Armonk, N.Y., USA) was used for statistical analysis. Kolmogorov-Smirnov test was used to evaluate data normality. Continuous variables are expressed as mean±standard deviation or median (range) and categorical variables as absolute frequency and percentage. The differences were considered statistically significant with a p-value <0.05. Comparisons of continuous variables between subgroups were assessed using a t-test or Mann-Whitney U test. Comparison of proportions for categorical variables between subgroups used chi-square test procedures. Associations between continuous variables used Pearson or Spearman correlation. Power of the study based on normal approximation was 46.1% and normal approximation with continuity correction was 38%.

RESULTS

The study involved 204 children (114 boys), with a median age of 8.4 (1.1-17.3) years, a mean BMI SDS of -0.44±1.47, median C-peptide value of 0.43 (0.05-2.99) ng/ml, and a mean HbA1c value of 12.1±2.5% at diagnosis. Diabetic ketoacidosis was found in 50.5% of the children (n=103). Autoantibodies were positive in 154 children (75.5%). C-peptide levels, median age and mean BMI SDSs were not statistically different according to autoantibody status (Data not shown).

The overall frequency of detectable C-peptide was 98.5%. Preserved C-peptide (i.e., ≥0.6 ng/mL) was observed in 32.8% (n=67) of the children. There were no significant intergroup differences regarding the presence of autoantibodies. 30.7% of the boys had preserved C-peptide, compared to 35.6% of the girls (p=0.464) (Table 1). The proportion of participants with preserved C-peptide was higher when onset had occurred at >5 years of age compared with ≤5 years of age (38.5% vs 19.7%, p=0.009). Patients with preserved C-peptide levels were older at onset [10.4 (1.9-16.5) vs 7.5 (1.1-17.3) yr, p<0.001], more likely to be pubertal (61.2% vs 22.6%, p<0.001), had a higher BMI SDS (0.03±1.37 vs -0.67±1.47, p=0.001), presented less frequently with DKA (21.4% vs. 78.6%, p<0.001) and had a lower HbA1c level (11.5±2.8% vs 12.4±2.2%, p=0.021), compared with the non-preserved C-peptide group. Preserved C-peptide was observed in 19.7, 51.5, 60, 60, and 66.7%, respectively, of

Table 1: Demographics and clinical characteristics of patients by preservation of C-peptide.

Demographics and clinical characteristics	Non-preserved C-peptide (n=137)	Preserved C-peptide (n=67)	P value
Gender			0.464
Female	58 (64.4)	32 (35.6)	
Male	79 (69.3)	35 (30.7)	
Age (yr)			**0.009**
≤5	49 (80.3)	12 (19.7)	
>5	88 (61.5)	55 (38.5)	
Puberty			**<0.001**
Prepubertal	106 (80.3)	26 (19.7)	
Pubertal	31 (43.1)	41 (56.9)	
Diabetic ketoacidosis	81 (78.6)	22 (21.4)	**<0.001**
Age (yr)	7.5 (1.1-17.3)	10.4 (1.9-16.5)	**<0.001**
Body mass index SDS	-0.67±1.47	0.03±1.37	**0.001**
pH	7.26 (6.8-7.5)	7.35 (7-7.4)	**<0.001**
C-peptide (ng/ml)	0.31 (0.05-0.59)	0.92 (0.6-2.99)	**<0.001**
Hemoglobin A1c (%)	12.4±2.2	11.5±2.8	**0.021**
Presence of autoantibodies			0.372
No	31 (62.0)	19 (38.0)	
Yes	106 (68.8)	48 (31.2)	
Overweight/obese			0.06
No	117 (70.1)	50 (29.9)	
Yes	20 (54.1)	17 (45.9)	

Data presented as number (%) or mean±standard deviation or median (range).

children at Tanner stages 1 (i.e., prepubertal), 2, 3, 4, and 5 (p<0.001).

There were 37 (18.1%) overweight or obese children. The proportion of individuals with preserved C-peptide levels increased with increasing BMI, but the difference did not reach statistical significance (29.9% to 45.9%, p=0.06) (Table 1). Patients who were overweight or obese had higher C-peptide levels at onset [0.57 (0.05-2.99) vs 0.41 (0.05-2.58) ng/ml, p=0.01]. In contrast, no significant among-group differences in gender, age, pubertal status, autoantibody status, the frequency of patients with DKA, pH, or HbA1c level were evident between the two groups (Table 2).

C-peptide level positively correlated with BMI-SDS (r_s=0.24, p=0.001), age (r_s=0.42, p<0.001) and pH (r_s=0.39, p<0.001). There was a negative correlation between HbA1c and both C-peptide level and BMI SDS (r_s=–0.2, p=0.004 and r=-0.16, p=0.025, respectively).

DISCUSSION

In this large, single-center study of more than 200 children with T1D, we examined the relationship between BMI and beta-cell function at diagnosis with the influence of age, among other factors. 18% of children were overweight or obese at T1D diagnosis. We demonstrated an overall frequency of detectable C-peptide of 98.5%, and approximately one-third of children with new-onset T1D had a significant residual beta-cell function. We further analyzed the factors associated with C-peptide levels and found that higher BMI SDS, older age, diagnosis during puberty, presentation without DKA were significantly related to the preservation of C-peptide levels at T1D diagnosis.

The American Diabetes Association defines T1D as "leading to absolute insulin deficiency," and clinicians usually consider the detection of residual beta-cell function as unexpected in this population (14). However, our data indicate that significant residual insulin secretion is present in one out of three children at T1D diagnosis. Similar results have been reported from several other studies (6, 8, 15). As expected, a statistically lower frequency of C-peptide preservation was observed in children with DKA compared to those without, and preserved C-peptide was associated with lower HbA1c (16). These findings highlight the significance of early diagnosis and the importance of the therapies to preserve residual beta-cell function in patients with T1D.

The accelerator hypothesis indicates that obesity-driven insulin resistance in genetically predisposed individuals leads to beta-cell autoimmunity and accelerates the clinical manifestation of diabetes (17). Increased insulin resistance associated with weight excess is characterized by increased secretory demand in beta-cells, potentially detrimental to beta-cell function (18). This phenomenon may lead to an earlier manifestation of T1D when the individuals have a higher beta-cell reserve than the others. In our study,

Table 2: Demographics and clinical characteristics of patients by weight group

Demographics and clinical characteristics	Lean (n=167)	Overweight/obese (n=37)	P value
Gender			0.117
Female	78 (86.7)	12 (13.3)	
Male	89 (78.1)	25 (21.9)	
Age (yr)			0.107
≤5	54 (88.5)	7 (11.5)	
>5	113 (79.0)	30 (21.0)	
Puberty			0.687
Prepubertal	107 (81.1)	25 (18.9)	
Pubertal	60 (83.3)	12 (16.7)	
Diabetic ketoacidosis	87 (84.5)	16 (15.5)	0.330
Age (yr)	8.5 (1.1-17.3)	8.1 (1.5-17)	0.889
pH	7.29 (6.8-7.5)	7.33 (6.9-7.43)	0.125
C-peptide (ng/ml)	0.41 (0.05-2.58)	0.57 (0.05-2.99)	**0.01**
Hemoglobin A1c (%)	12.2±2.4	11.6±2.5	0.182
Presence of autoantibodies			0.652
No	42 (84.0)	8 (16.0)	
Yes	125 (81.2)	29 (18.8)	

Data presented as number (%) or mean±standard deviation or median (range).

the overweight/obese group included a slightly larger proportion of children with preserved C-peptide levels. Another possible explanation for this may be the relatively greater insulin resistance leading to a compensatory increase in C-peptide levels in these patients (6). On the other hand, a higher BMI might also represent a milder presentation status of T1D.

In line with our findings, several studies reported that preservation of C-peptide levels was more frequently determined in overweight or obese children at T1D diagnosis (19). Ludvigsson et al. reported that patients with T1D and higher BMI had higher C-peptide levels at diagnosis. However, they suggested a more rapid loss of C peptide during the first years after diagnosis (20). Greenbaum et al. demonstrated that BMI was not associated with preserved fasting C-peptide levels in T1D children within one year of diagnosis. However, during follow-up, they noted that overweight/obesity was related to C-peptide preservation (21). Sosenko et al. showed that higher weight was positively associated with C-peptide levels in a pediatric cohort at and soon after diagnosis (8). As our study included only children with new-onset T1D, we think that this data is a precise reflection of the balance between obesity-induced insulin resistance and insulin secretion capacity, leading to the clinical manifestation of T1D. Many factors could alter beta-cell function and BMI after disease onset, including insulin therapy. Variable use of fasting or prandial C-peptide levels and differences in the prevalence of overweight and obesity might also explain conflicting results among studies.

Consistent with our data, several studies have shown that older age and puberty are associated with higher C-peptide levels at diagnosis (22, 23). Younger children have an overall less functional beta-cell mass, and a younger diagnosis leads to a more significant beta-cell loss (15, 24). In this study, age did not influence the relationship between BMI and T1D onset, as a higher BMI was not associated with younger age at diagnosis. Previous studies that assessed this relationship have yielded controversial results. While some studies confirmed that heavier children developed diabetes at a younger age, other studies did not find this relationship (25, 26). It was suggested that there is a threshold on the effect of BMI upon the age of diabetes onset (19). Differences in age distribution may also contribute to variability among studies as age at diagnosis significantly impacts the preservation of C-peptide levels, and the prevalence of obesity increases with age (27).

In accordance with other studies, C-peptide level correlated positively with BMI SDS but negatively with HbA1c, suggesting a shorter or milder preclinical course in those with higher residual beta-cell reserve at presentation (8, 28). In addition, the negative correlation between BMI SDS and HbA1c indicates that children with higher BMI are diagnosed with T1D at an earlier stage with more significant beta-cell function.

In conclusion, overweight or obese children had more residual beta-cell function at diagnosis than lean children. Preservation of C-peptide levels is related to age, pubertal status, pH, HbA1c, and BMI at diagnosis. Our work provides supportive evidence for the crucial role of BMI in T1D. Future efforts should focus on the relationship between C-peptide and BMI to preserve residual beta-cell function for as long as possible. These findings also have important clinical implications indicating the importance of a precise evaluation of C-peptide levels in obese youth with diabetes.

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None.

Author Contributions

All authors contributed to the study conception and design. Material preparation and data collection were performed by **Emine Ayça Cimbek, Mehmet Aykut Öztürk,** and **Gülay Karagüzel,** and analyzed by **Emine Ayça Cimbek,** and **Gülay Karagüzel.** The first draft of the manuscript was written by **Emine Ayça Cimbek,** and all authors commented on previous versions of the manuscript. All authors have read and approved the final manuscript. All agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflict of Interest

Competing interests: The authors have no conflicts of interest to declare that are relevant to the content of this article.

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Ethical Approval

The Institutional Review Board approved the study (Karadeniz Technical University Ethics Committee: 2022-11-10-24237859-163). All procedures were done in agreement with Helsinki declaration for studies on human subjects.

Consent to participate: N/A

Consent for publication: This retrospective study did not require written informed consent.

Availability of data and material: The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Code availability: N/A

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Peer Review Process

Extremely peer-reviewed and accepted.

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