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Research article

Prevalence of Obesity and Metabolic Syndrome in Children with Type 1 Diabetes: A comparative assessment based on criteria established by WHO, IDF and NCEP

Short title: Prevalence of MetS in T1D

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What is already known on this topic?
There are few studies reporting the prevalence of obesity and metabolic syndrome in the pediatric patient group with type 1 diabetes (T1D), but there is no reported data from Turkey. Diagnosis of metabolic syndrome in early ages in T1D patients is very important to prevent and manage macrovascular complications. Nevertheless, determining the presence of metabolic syndrome in T1D is difficult and it is not clear which criteria are most suitable for its diagnosis.

What this study adds?
Our study reports the prevalence of obesity and metabolic syndrome in children with type 1 diabetes in our region. Also, this study comparatively assesses widely accepted and used diagnostic criteria for metabolic syndrome established by IDF, WHO and NCEP.

Abstract
Aim: To determine the prevalence of obesity and metabolic syndrome (MetS) in children and adolescents with type 1 diabetes (T1D) and to compare widely accepted and used diagnostic criteria for metabolic syndrome established by IDF, WHO and NCEP-ATPIII.
Material and Method: We conducted a descriptive, cross sectional study including T1D patients between 8-18 years of age. Modified criteria of IDF, WHO and NCEP-ATPIII were used to determine the prevalence of MetS. Hospital records were analyzed to determine related risk factors with MetS.
Results: The study included 200 patients with T1D (52% boys). Of these, 18% were overweight/obese (BMI percentile ≥ %85). MetS prevalence was found as 10.5%, 8.5% and 13.5% according to IDF, WHO and NCEP criteria, respectively. There were no statistically significant differences in age, gender, family history of T1D and T2D, pubertal stage, duration of diabetes, A1C levels and daily insulin doses between patients with or without MetS. In a total of 36 overweight or obese T1D patients, the prevalence of MetS was 44.4%, 38.8% and 44.4% according to IDF, WHO and NCEP-ATPIII criteria, respectively.
Conclusion: Obesity prevalence of our T1D cohort is similar to healthy population in the same ages. Prevalence of MetS is higher in children and adolescents with T1D compared to the obese population in our country. Our study suggests that IDF criteria are more suitable for the diagnosis of MetS in children and adolescents with T1D.
Keywords: Type 1 Diabetes, Metabolic Syndrome, prevalence, WHO, IDF, NCEP-ATPIII

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Introduction

Type 1 diabetes (T1D) is a chronic disease characterized by absolute insulin deficiency due to immune-mediated destruction of pancreas beta cells. T1D has always been associated with a leaner phenotype. However, the number of obese patients with T1D is increasing related to raising obesity in worldwide (1,2). Metabolic syndrome (MetS), also called insulin resistance syndrome, on the other hand, is a cluster of diagnostic criteria including abdominal obesity, type 2 diabetes (T2D) and cardiovascular risk factors such as hypertension, dyslipidemia and nephropathy (3). Determining the frequency of MetS in patients with T1D means determining the frequency of coexistence of obesity, hypertension, dyslipidemia. Yet, there are scarce of studies in pediatric age with T1D group on prevalence of obesity and metabolic syndrome.

In the T1D population, while the incidence of microvascular complications is decreasing owing to intensive diabetes management, the macrovascular complications have been more commonly seen today, which is considered to be associated with the increasing incidence of obesity and MetS (4-8). This situation has led to the understanding that diagnosis of MetS and obesity is essential to improve the quality and duration of life in children and adolescents with T1D. For the diagnosis of MetS in childhood and adolescence, the International Diabetes Federation (IDF) criteria are globally accepted. World Health Organization (WHO) and the National Cholesterol Education Program - Adult Treatment Panel III (NCEP-ATPIII) criteria used for the diagnosis of MetS in the adult population can also be used for children and adolescents with some modifications. In the present study, we aimed to determine the prevalence of obesity and MetS in a large cohort of children and adolescents with T1D, and to compare widely accepted and used criteria for the diagnosis of MetS.

Research design and methods:

Ethics committee approval was received for this study from the local ethics committee of Faculty of Medicine, Samsun Ondokuz Mayıs University (2014-354).

Patients and data documentation: We conducted a descriptive, cross sectional study including a total of 200 T1D patients between 8-18 years of age who were followed up for at least six months. Clinical and laboratory data were obtained from the patients' medical records including age, sex, anthropometric measurements, duration of diabetes, daily insulin dose, metabolic control level, laboratory values (HbA1c, total cholesterol, HDL, LDL and triglyceride levels), comorbidities and treatments. History of T1D and/or T2D in first- and second-degree relatives was recorded. Average insulin doses for the intensive insulin treatment group were calculated by finding the total insulin dose of three days which were randomly selected from the previous month and divided by the patient's weight. The patients were evaluated for complications of diabetes and accompanying diseases. Existence of hypertension, prehypertension, microalbuminuria, retinopathy and neuropathy in addition to thyroid and coeliac disease were recorded. Patients who had other types of diabetes including T2D, maturity onset diabetes of the young and secondary diabetes were excluded from the study.

The patients' height, weight and waist circumference (WC) were measured and body mass index (BMI) was calculated. Overweight and obesity were defined as a BMI $\geq 85^{th}$ and $\geq 95^{th}$ percentile, respectively (9).

In order to establish the degree of metabolic control, the average of HbA1c levels measured through the last year was calculated. According to the average HbA1c levels, the patients were divided into three metabolic control groups: good, HbA1C < 7.5 %; moderate, HbA1c 7.5 - 9 %, and poor HbA1c > 9 % (1).

The patient groups whose anthropologic and clinical data were recorded at application, the third month of follow-up and the last control consisted mainly of patients who had ketoacidosis at application and patients who had just begun treatment. For this reason, the data obtained after the onset of disease and at the third month of treatment was accepted as baseline values. The evaluation at the last control was aimed to obtain the outcomes under treatment.

WHO and NCEP-ATPIII diagnostic criteria were used for MetS diagnosis in addition to MetS criteria which were published by IDF in 2005 for children and adolescents. WHO defines MetS as glucose intolerance, impaired glucose tolerance or diabetes mellitus, and/or insulin resistance, along with two or more of the components listed as: high blood pressure (≥ 140/90 mmHg), hypertriglyceridemia (≥ 150 mg/dl) and/or low HDL cholesterol (< 35 mg/dl in men and < 39 mg/dl in women), central obesity (waist/hip ratio > 0.9 in men and > 0.85 in women) and/or BMI >30 kg/m2 and microalbuminuria (urinary albumin excretion rate ≥ 20 µg/min or albumin/creatine ratio ≥ 30 µg/mg) (10). According to NCEP-ATPIII definition, a subject has the MetS if he or she has three or more of the following criteria: abdominal obesity (WC ≥ 102 cm in men and ≥88 cm in women), hypertriglyceridemia (≥ 150 mg/dl), low HDL cholesterol (< 40 mg/dl in men and < 50 mg/dl in women), high blood pressure (> 130/85 mmHg), and/or high fasting glucose (> 110 mg/dl) (11). Children over 8 years of age were eligible for the study because there were no well-defined criteria to diagnose MetS in children aged 6 to 10 years (12). According to IDF definition, a subject has MetS if he or she is between 6 to 10 years of age and has obesity >90th percentile as assessed by waist circumference. If the age is between 10 to 16 years, a subject has MetS if he or she has obesity >90th percentile (or adult cut-off if lower) as assessed by WC and has two or more of the following criteria: hypertriglyceridemia (≥150 mg/dl), low HDL cholesterol (<40 mg/dL), high blood pressure percentile for age, sex and height, raised fasting glucose (>100 mg/dL). Since WHO and NCEP-ATPIII criteria were formulated for adults; these criteria were used with pediatric percentiles so that they could be applied to children. These two criteria groups were thus modified for use in pediatric and

adolescent age groups. Impaired glucose tolerance or impaired fasting glycemia or existence of T2D which are part of the mentioned criteria were accepted as positive for our T1D patient group. Patients were examined for the existence of either of the two remaining criteria. Dyslipidemia was accepted as HDL below 50 mg/dL and triglyceride above 150 mg/dL. Pediatric percentiles were used for hypertension, WC and BMI (9). Patients with MetS according to IDF criteria were compared in terms of demographical and clinical data.

Statistical analysis: All statistical analyses were performed using SPSS software version 21. Significant differences were analyzed using the Student's t-test for continuous variables and Chi-Square (ki^2) or Fisher's exact test for categorical variables.

Results

The study group consisted of 200 T1D patients whom average age was 13.8 ± 2.8 years, duration of diabetes 4.6 ± 3.3 years, 52 % male and 87 % pubertal. Average HbA1c was 8.40 ± 1.63 % and average insulin dose was 0.87 ± 0.26 U/day. In the family history, T1D and T2D were detected in 17.5% and 44% of the patients, respectively. Only 3 patients had insulin pump, all the patients (n:197) were on multiple insulin injections. Of the 200 patients with T1D, according to HbA1c levels % 26.5 had good, % 37 moderate and % 36.5 had poor metabolic control. Of the 200 patients with T1D, 19 (9.5%) were overweight and 17 (8.5%) were obese.

Prevalence of MetS in our T1D cohort was found as 10.5 %, 8.5 % and 13.5 % according to IDF, WHO and NCEP-ATPIII criteria, respectively. Figure 1 shows the numbers of patients with MetS diagnosis according to different diagnostic criteria.

In a total of 36 overweight or obese T1D patients, the prevalence of MetS was 44.4%, 38.8% and 44.4% according to IDF, WHO and NCEP-ATPIII criteria, respectively.

Table 1 depicts the clinical characteristics of MetS positive versus negative T1D patients according to IDF criteria. There were no statistically significant differences in age, gender, family history of T1D, pubertal stage, duration of diabetes, HbA1c levels and daily insulin doses between patients with or without MetS but the difference was significant concerning family history of T2D and clinical and laboratory components of MetS. LDL-cholesterol and triglyceride concentrations were higher in patients with MetS ($p < 0.001$). When demographical and clinical data of patients with and without MetS according to WHO and NCEP-ATPIII criteria are evaluated, similar results to IDF criteria have been obtained (data not shown).

As shown in Table 2, the BMI SDS values of all patients had increased under intense insulin treatment following diagnosis according to IDF, WHO and NCEP-ATPIII criteria. The BMI SDS values of the group diagnosed with MetS according to IDF, WHO and NCEP-ATPIII criteria, higher than the non-MetS group in all three evaluations with significant statistically differences.

All cases diagnosed as MetS according to all three criteria groups had BMI values above the 50th percentile at the diagnosis of T1D.

Discussion

There is no data on the prevalence of obesity in children and adolescents with T1D in Turkey. In our study group comprising 200 children with T1D between 8 and 18 years, total prevalence of overweight and obesity was found to be 18%. The prevalence of overweight and obesity in schoolchildren and adolescents from different regions of our country has been reported in the range of 12.8-20.2% (13-17). Accordingly, the present study has shown that obesity prevalence of our T1D cohort was similar to that of the general population in Turkey. Studies from other countries have indicated that the increased incidence of overweight and obesity in T1D population has been correlated to the status of general population (18-22). Although the traditional belief is that patients with T1D are normal or thin, overweight and obesity are increasing parallel to the normal population as a result of investigations performed on T1D population. Intense insulin therapy and weight gain due to the anabolizing and lipogenic effect of insulin are thought to be responsible. Additionally, the change in the nutrition habits and shift to sedentary life style which are held responsible from a global increase in overweight and obesity have also affected the young population with T1D. Nowadays T1D patients are more obese compared to the past, which has been associated with intense insulin treatment. EDIC study reveals that the incidence of obesity in T1D patients has significantly increased due to widespread intense insulin treatment following DCCT (22-24). Some authors indicated that being female was a risk factor for a higher BMI SDS 6 years after diabetes onset (25). All of our patients had gained weight at the time of diagnosis, third month of follow up and the last visit. Since the patients could have lost weight before diagnosis, the BMI SDS values at the third month follow up and the last visit were evaluated and a striking weight gain has been noted. This reflects the effect of intense insulin treatment. All the patient gained weight, however weight gain was more prominent in the MetS positive group. Another striking point is that the BMI and BMI SDS values in the MetS positive group was higher than the MetS negative group in a statistically significant manner since the beginning.

Data on MetS prevalence in patients with T1D is controversial. The prevalence of MetS was evaluated using 3 criteria groups and in 200 T1D children; it was 10,5 % according to IDF, 8,5 % according to WHO and 13,5 % according to NCEP-ATPIII. Although there are no studies that report the prevalence of MetS in children and adolescents with T1D in Turkey, MetS seems to be more common in T1D population when compared to the obese population. The small number of studies comparing the prevalence of MetS in T1D children and

adolescents and the results vary between countries. In a study where 115 T1D patients between 5-16 years of age were investigated, MetS prevalence was found as 13.2% according to IDF. The researchers found a significantly low incidence of MetS for that study population (26, 27). Pinhas et al reported a 7,1% prevalence of MetS in 326 T1D patients whose median age was 18,5 (19).

The prevalence of MetS in overweight and obese children and adolescents in our country has been reported as 20%-38% according to WHO, IDF and NCEP-ATPIII criteria (28-30). In our study, the incidence of MetS in overweight and obese patients was 41,7 % according to IDF, 38,3 % according to WHO and 47,2 % according to NCEP-ATPIII criteria.

Although it is widely accepted that it is necessary to diagnose MetS in early stages of T1D, the main problem is the inadequacy of the criteria for the diagnosis of MetS in T1D patients. NCEP-ATPIII criteria have provided the highest prevalence in our study (13,5 %) since NCEP-ATPIII allows diagnosis by three positives out of five criteria with no mandatory prerequisites. Since diabetes is accepted as positive, two out of the remaining of four criteria are enough and these criteria are already present in patients diagnosed using IDF criteria. As such, NCEP-ATPIII includes both the IDF criteria group and the group which does not meet the waist circumference group, not obese according to WC, but positive for two other criteria. Waist circumference of the group which meets NCEP-ATPIII criteria but not the IDF criteria is below 90^{th} percentile while the two criteria they meet is either hypertriglyceridemia, low HDL or hypertension. Since there are no primary criteria in NCEP-ATPIII and it evaluates the WHO dyslipidemia criteria as two distinct criteria, it encompasses all cases diagnosed using WHO and IDF.

The results of our study are evaluated according to IDF criteria, we realized that the incidence of MetS is higher in the group where T1D accompanies overweight and obesity compared to those who do not have T1D. The incidence of MetS is similar between overweight and obese individuals independent of T1D, according to WHO criteria. This discrepancy is caused by the difference between the definition of MetS. Impaired glucose tolerance or T2D is a prerequisite for MetS in WHO criteria, so it is understood that MetS prevalence will not change if the criteria is actualized as T1D. On the other hand, obesity as determined by WC is a prerequisite for MetS while impaired glucose tolerance and T2D are secondary criteria. Since this criterion is met by all patients in addition to obesity in our study population which consisted of T1D patients, the ratio was found to be high. NCEP-ATPIII criteria includes the IDF criteria and has no prerequisites hence the highest incidence was found using these criteria.

On the other hand, insulin resistance and/or diabetes is the mandatory primary criterion for WHO and our T1D patient group meets this criterion. WHO criteria also include microalbuminuria which has the highest sensitivity for MetS in adulthood however, our study group, because of its age, had the lowest prevalence for this criterion since these complications had not occurred yet (31-33). In the study group, there were 25 patients whose BMI was below 95th percentile while waist circumference was above 90 percentile, which caused IDF and NCEP-ATPIII to diagnose more MetS with T1D. All patients who were diagnosed positive using WHO criteria meet NCEP-ATPIII criteria, too.

The WHO criteria include microvascular complications which are rare in childhood and the NCEP criteria do not include a primary criterion while diagnosing non-obese patients according to waist circumference as MetS because the existence of diabetes is considered as a direct criterion. Due to these reasons, these criteria do not seem to be useful for the diagnosis of MetS in children and adolescents with T1D. Using IDF criteria seems more suitable because obesity is a prerequisite and they include accepted criteria for childhood (10-12).

Study Limitations

Our study has several limitations and strengths. The main limitation is the absence of accepted clinical and laboratory criteria for the diagnosis of MetS in children and adolescents with T1D children. We had to use modified criteria to determine the prevalence. On the other hand, using and comparing three different modified criteria is the strength of our study. Also, the strength of our research consists in the existence of accurate data which adds the information of MetS prevalence in children and adolescents with T1D.

Conclusion

Overweight and obesity prevalence of the group with T1D was similar to the population of the same age group in our country, but prevalence of MetS was found to be higher than the community. Except for the components of metabolic syndrome, the other clinical and laboratory parameters were not helpful for prediction. It has been observed that all children and adolescents with T1D gained weight under intense insulin treatment however weight gain was more prominent in the MetS positive group. It is clear that appropriate modification of the criteria is required for the early detection of MetS in children and adolescents with T1D, however our study suggests that IDF criteria are more suitable for the diagnosis of MetS in children and adolescents with T1D.

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this study were presented in poster form at the European Society of Pediatric Endocrinology Congress, Barcelona/Spain, 01-03 October, 2014.

Ethics

Ethics Committee Approval: The local ethics committee of Faculty of Medicine, Samsun Ondokuz Mayıs University (Approval number: 2014-354).

Informed Consent: Written informed consent was obtained from the parents of the patients who participated in this study.

Peer-review: Externally peer reviewed.

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Table-1 Comparison of the demographic and clinical findings of T1D patients with and without metabolic syndrome according to IDF criteria (10)

Characteristics T1D (n:200)	MetS positive n: 21 (10.5 %)	MetS negative N:179 (89.5 %)	p-value
Gender (Male) (n,%)	10 (47.6)	94 (52.5)	0.671
Age (years) (Mean±SD)	13.7 ± 3.3	13.8 ± 2.8	0.995
Pubertal Status (n, %) Prepubertal Postpubertal	 4 (19) 17 (81)	 22 (12.3) 157 (87.5)	 0.488
Family History (n, %) T1D T2D	 3 (14.3) 13 (61.9)	 32 (17.9) 75 (41.8)	 1 1
Duration of diabetes (mo)	57.3±45.8	54.9±39.2	0.949
Waist circumference (cm) (Mean±SD)	82.9±10.8	67.9±7.7	<0.001
Waist circumference SDS (Mean±SD)	2.2±0.6	0,3±0,97	<0.001
Insulin Dose (U/kg) (Mean±SD)	0.9±0.2	0.9±0.3	0.932
Status of Metabolic Control (HbA1c %) (n,%) Good (≤7,5) Moderate (7,5-9,0) Poor (≥9,0)	 4 (19) 8 (38.1) 9 (42.9)	 49 (27.4) 66 (36.9) 64 (35.8)	 0.684
Existence of Acanthosis (n,%)	5 (23.8)	6 (3.4)	0.002
Comorbidities (n,%) Prehypertension Hypertension Dyslipidemia Microalbuminuria	 2 (9.5) 14 (66.7) 12 (21.1) -	 5 (2.8) 10 (5.6) 45 (78.9) 8 (4.5)	 <0.001 <0.001 0.004 1.000
Existence of Additional Disease (n,%) Thyroid autoantibody positive Thyroid disease Coeliac disease	 3 (14.3) 1 (4.8) -	 25 (14) 19 (10.6) 4 (2.2)	 1.000 0.701 1.000
HbA1c levels (Mean±SD) Recent year At the most recent control	 8.8±1.4 8.6±1.5	 8.6±1.5 8.4±1.6	 0.374 0.439
Lipid Profile (Mean±SD) Triglyceride (mg/dL) HDL cholesterol (mg/dL) LDL cholesterol (mg/dL)	 130.1±60.4 55.4±15.4 106.2±20.3	 85.2±42.0 62.1±15.6 77.0±24.7	 <0.001 0.050 <0.001

Table-2 Changes in BMI SDS values over time among MetS positive and negative groups according to IDF, WHO and NCEP-ATPIII criteria

Time	Criteria	BMI SDS		P value
		MetS (+)	MetS (-)	
At time of diagnosis	IDF	0.3±1.6	-0.8±1.7	0.004
	WHO	-0.1±1.4	-0.7±1.7	<0.001
	NCEP-ATPIII	0.4±1.8	-0.8±1.7	<0.001
At third month of follow up	IDF	1.0±0.3	-0.7±1.1	0.003
	WHO	0.8±1.6	0.03±1.4	<0.001
	NCEP-ATPIII	1.1±1.3	-0.4±1.4	<0.001
During study period	IDF	1.3±0.8	-0.1±1.1	<0.001
	WHO	1.1±0.8	-0.1±1.1	<0.001
	NCEP-ATPIII	1.2±1.0	-0.15±1.0	<0.001

BMI SDS: Body mass index SDS, MetS: Metabolic syndrome, IDF: International Diabetes Federation, WHO: World Health Organisation, NCEP-ATPIII: National Cholesterol Education Program - Adult Treatment Panel III

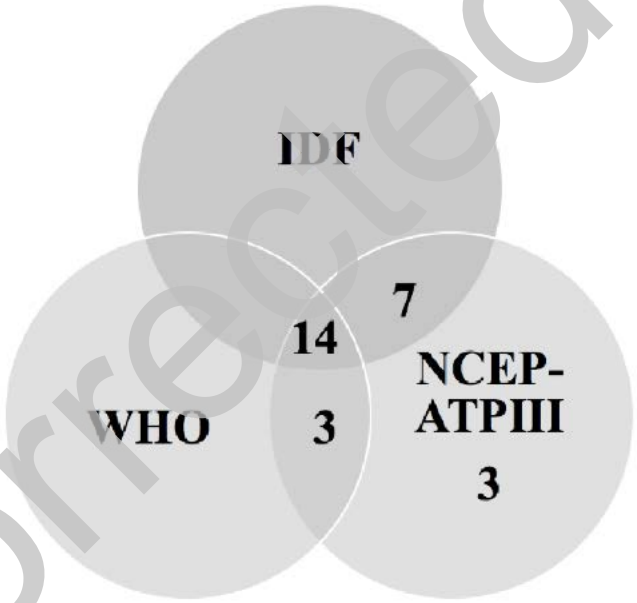

Figure 1: The numbers of patients with MetS diagnosis based on different diagnostic criteria