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Characteristics of Turkish children with Type 2 diabetes at onset: a multicentre, cross-sectional study

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Abstract

Aims To describe the baseline clinical and laboratory findings and treatment modalities of 367 children and adolescents diagnosed with Type 2 diabetes in various paediatric endocrinology centres in Turkey.

Methods A standard questionnaire regarding clinical and laboratory characteristics at onset was uploaded to an online national database system. Data for 367 children (aged 6–18 years) newly diagnosed with Type 2 diabetes at 37 different paediatric endocrinology centres were analysed.

Results After exclusion of the children with a BMI Z-score < 1 SD, those with genetic syndromes associated with Type 2 diabetes, and those whose C-peptide and/or insulin levels were not available, 227 cases were included in the study. Mean age was 13.8 ± 2.2 (range 6.5–17.8) years, with female preponderance (68%). Family history of Type 2 diabetes was positive in 86% of the children. The mean BMI was 31.3 ± 6.5 kg/m^2 (range 18.7–61) and BMI Z-score was 2.4 ± 0.8 (range 1–5). More than half (57%) of the children were identified by an opportunistic diabetes screening due to existing risk markers without typical symptoms of diabetes. Only 13% (n = 29) were treated solely by lifestyle modification, while 40.5% (n = 92) were treated with metformin, 13% (n = 30) were treated with insulin, and 33.5% (n = 76) were treated with a combination of insulin and metformin initially. Mean HbA_{1C} levels of the insulin and combination of insulin and metformin groups were 98 (11.1%) and 102 mmol/mol (11.5%), respectively, and also were significantly higher than the lifestyle modification only and metformin groups mean HbA_{1C} levels (70(8.6%) and 67 mmol/mol (8.3%), respectively).

Conclusions An opportunistic screening of children who are at high risk of Type 2 diabetes is essential, as our data showed that > 50% of the children were asymptomatic at diagnosis. The other important result of our study was the high rate of exclusion from the initial registration (38%), suggesting that accurate diagnosis of Type 2 diabetes in youth is still problematic, even for paediatric endocrinologists.

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Introduction

Type 2 diabetes has become a serious health problem in children and adolescents as the prevalence of obesity has increased in this age group [1–5]. The SEARCH for Diabetes

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What's new?

- Female gender and positive family history were strongly associated with Type 2 diabetes in Turkish children as well as children in western countries.
- More than half (57%) of the participants were identified by opportunistic diabetes screening due to existing risk markers, without typical symptoms of diabetes.
- Approximately half of the children (47%) with Type 2 diabetes were treated with insulin while only 13% were treated solely by lifestyle modification.

in Youth study indicated a significant increase in the incidence of Type 2 diabetes (from 9.0 cases per 100 000 youths per year in 2002–2003 to 12.5 cases per 100 000 youths per year in 2011–2012; annual increase, 7.1%) in the USA [1]. Among new cases of paediatric diabetes in the USA, 8–45% are reported to be Type 2 diabetes [2–5]. Although the prevalence of Type 2 diabetes in children and adolescents in Europe is lower than in the USA [6,7], screening studies from Europe reported an increase from 0.4 to 1% in the prevalence of Type 2 diabetes among obese children ≥ 12 years of age [8,9]. The incidence of Type 2 diabetes in children and adolescents in Turkey remains unknown. A single-centre study from Turkey compared the incidence of Type 2 diabetes among children and adolescents across three time periods and found statistically significant increases in frequency of 1.9, 2.4 and 7.9% during 1999–2004, 2005–2010 and 2011–2016, respectively [10].

The chronic complications of diabetes such as nephropathy and retinopathy are more common at diagnosis or appear earlier in the course of Type 2 diabetes than in Type 1 diabetes [11]. Thus, screening for and early detection of Type 2 diabetes are very important. On the other hand, as the number of children with Type 2 diabetes increases, it is necessary to differentiate Type 2 diabetes from other types of diabetes to administer the most appropriate treatment. The increased prevalence of obesity in children newly diagnosed with Type 1 diabetes and lack of precise diagnostic parameters for Type 2 diabetes are the major confounders to accurate diagnoses of Type 2 diabetes.

In this multicentre cross-sectional study, we retrospectively evaluated the baseline clinical and laboratory findings and treatment modalities of children and adolescents diagnosed with Type 2 diabetes in 37 different paediatric endocrinology units across Turkey.

Methods

Data collection

A common case recording form was created that covered demographic features as well as clinical and laboratory findings relating to children with Type 2 diabetes at the time of diagnosis. The results were uploaded to the registry system of the National Pediatric Endocrinology and Diabetes Association (http://cedd.saglik-network.org). The study was approved by the Ethics Committee of Gulhane Military Medical Academy, Ankara, Turkey. Paediatric endocrinologists taking care of the children and adolescents with Type 2 diabetes in paediatric endocrinology units were asked to register participants using the online registry system CEDD Net Web Registry System website (www.cedd.saglik-network.org).

The files of 367 children aged 6–18 years diagnosed with Type 2 diabetes between April 2015 and May 2016 in 37 different paediatric endocrinology units in Turkey were retrospectively evaluated. The participating centres represented all seven of the geographical regions of Turkey.

Participants

Diagnosis of diabetes was based on the criteria of the American Diabetes Association [12]. Diagnostic criteria for diabetes included HbA_{1C} ≥ 48 mmol/mol (≥ 6.5%), random glucose > 11.1 mmol/l, 2-hour post-challenge glucose ≥ 11.1 mmol/l or a fasting glucose ≥ 7.0 mmol/l; however, oral glucose tolerance test (OGTT) results were unavailable. The children who met diagnostic criteria for diabetes, with a BMI Z-score of ≥ 1 SD for age and sex with negative pancreatic autoantibodies, and those whose pancreatic autoantibodies were not available but who had a fasting C-peptide level > 1.2 ng/ml (0.4 nmol/l) at the time of diagnosis [13], were included. The children with a BMI-Z score < 1 SD, those with genetic syndromes associated with Type 2 diabetes, and those whose C-peptide and/or insulin levels were not available, were excluded.

Measurements

At the time of enrolment, clinical characteristics data were collected from medical records and from interviews with the children and/or their parents. The data collected included information about the presentation and diagnosis of Type 2 diabetes, treatment at the time of diagnosis, and measurements taken by the healthcare provider at the time of diagnosis (height, weight, and blood pressure where available). Additional information including age, gender, family history of diabetes and other medical conditions associated with diabetes was collected. BMI SD scores for age and gender were calculated using an online program (ÇEDD ÇÖZÜM) based on weight, height and BMI percentile curves for Turkish children [14]. Obesity and overweight were defined using the growth references of BMI-for-age Z-score for 5–19 years developed by the WHO: thinness < −2 SD; overweight > +1 SD; obesity > +2 SD [15]. C-peptide level (ng/ml), presence of autoantibodies (islet cell, glutamic acid decarboxylase, insulin), presence of ketone bodies, pH and

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HCO3 levels, serum lipid levels at the time of diagnosis, presence of macro/microalbuminuria and treatment modalities (diet, oral antidiabetic drug, insulin) were collected from medical records. The 2011 Expert panel integrated guidelines for cardiovascular health and risk reduction in children and adolescents [16] were used to characterize lipid abnormalities. Accordingly, the presence of at least one of the following was accepted as dyslipidaemia: an LDL-cholesterol level of ≥ 3.4 mmol/l, an HDL-cholesterol level of < 1 mmol/l, or a triglyceride level of ≥ 1.5 mmol/l.

Statistical analyses

All analyses were conducted using SPSS version 22 (IBM SPSS Statistics for Windows, Version 22.0. IBM Corp, Armonk, NY, USA). Frequencies and percentages represented the descriptive statistics for categorical variables. For continuous variables, mean and ± SD values were used if variables had normal distribution; median values were used if variables did not have normal distribution. For categorical variables, χ^2 test was used, and for continuous variables t-test was used when the data was normally distributed. Kruskal-Wallis was used for comparing three or more groups and Mann-Whitney U-test was used for comparing two groups of continuous variables in the case of non-normal distribution. Bonferroni correction was used to determine the significance level in six comparisons with a *P*-value of 0.008 and in three comparisons with a *P*-value of 0.0125.

Results

Participants

A total of 367 children were registered. After exclusions, a total of 227 children (61%) were included in the analysis (Fig. 1). The mean age, BMI, BMI SD, HbA_{1C} levels and the median fasting plasma glucose, insulin and C-peptide levels were significantly higher for those children who were eligible than for those who were not. Among the non-eligible cases, the ratio of prepubertal cases was significantly higher in contrast to the ratio of the presence of acanthosis nigricans and classical symptoms of diabetes such as polydipsia, polyuria and weight loss. Table 1 shows the comparison of clinical and laboratory features of eligible and non-eligible cases.

The majority of the 227 cases involved female children (68%) and a positive family history of Type 2 diabetes (86%). Birth weight data were available for 170 children: 67% were reported to be appropriate for gestational age, 25% large for gestational age, and 8% small for gestational age. The distribution across small, normal and large birth size was not statistically different between the gender groups ($P = 0.77$). The majority of children (93%) were in Tanner stage 4 or 5. Even though they had no diabetes symptoms, most children ($n = 130$, 57%) were identified by diabetes testing, which was conducted because they were considered to be at high risk of Type 2 diabetes due to a positive family history of Type 2 diabetes in a first- or second-degree relative (86%), and/or presence of acanthosis nigricans (81%), in addition to overweight or obesity. There were no differences

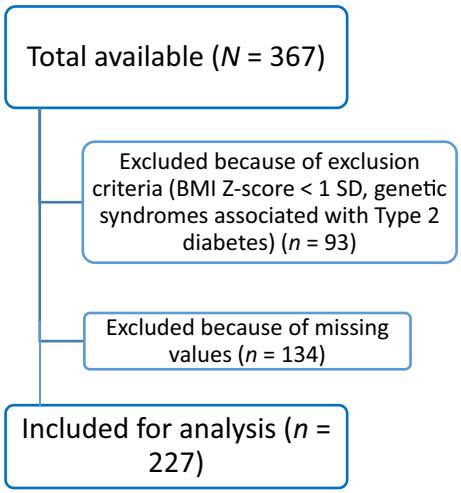


FIGURE 1 Study flow diagram.

Table 1 Comparison of clinical and laboratory features of the eligible and non-eligible cases

	Eligible cases (*N* = 227)	Non-eligible cases (*N* = 140)	*P*-value
Age (years)	13.8 ± 2.2 (6.5–17.8)	12.8 ± 3.1 (2.5–17.6)	0.001
BMI (kg/m^2)	31.3 ± 6.5 (18.7–61)	26.5 ± 5.9 (14.8–43)	<0.001
BMI SD	2.4 ± 0.8 (1–5)	1.7 ± 1.2 (-1.5–3.7)	<0.001
Tanner stage 1 (%)	7 (*n* = 15)	18 (*n* = 26)	0.001
Presence of acanthosis nigricans (%)	69 (*n* = 157)	45 (*n* = 64)	<0.001
Presence of diabetic symptoms (%)	43 (*n* = 97)	27 (*n* = 38)	0.001
Fasting plasma glucose (mmol/l)	12.5 (7.6–16.7, range 4.2–44.5)	7.9 (7–15.2) (range 4.1–36)	<0.001
Fasting insulin level (μU/ml)	21.4 (11.96–40.2) (range 1.18–330)	14.6 (8.8–29.4) (range 1.3–44)	<0.001
Fasting C-peptide (ng/ml)	3.5 (2.66–5.1) (range 0.61–22.2)	2.5 (1.9–4.2) (range 0.3–13.2)	0.009
HbA_{1c} (mmol/mol) (%)	84 ± 5 (9.8 ± 2.6) [range 48–178 (6.5–18)]	60 ± 11 (7.6 ± 3.2) [range 20–173 (4–18.3)]	<0.001

Age, BMI, BMI Z-score, HbA_{1C} expressed as mean (SD); fasting blood glucose, insulin, C-peptide levels as median (25th to 75th percentile), all others as percentages.

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Table 2 Clinical and laboratory features by gender at diagnosis

	Overall (*N* = 227)	Female (*N* = 155)	Male (*N* = 72)	*P*-value
Age (years)	13.8 ± 2.2	13.7 ± 2.2	14.1 ± 2.2	0.628
BMI (kg/m^2)	31.3 ± 6.5	31.6 ± 6.6	30.7 ± 6.2	0.362
BMI SD	2.4 ± 0.8	2.5 ± 0.8	2.2 ± 0.7	**0.012**
Tanner stages 4–5	212 (93%)	147 (94%)	65 (90%)	0.158
Presence of acanthosis nigricans	157 (69%)	103 (66%)	54 (75%)	0.194
Presence of diabetes symptoms	97 (43%)	60 (38.7%)	37 (51.3%)	0.07
Size at term birth	*n* = 170	*n* = 110	*n* = 60	0.77
Small (SGA) (< 2500 g)	13 (8%)	9 (8%)	4 (7%)	
Normal (AGA) (2500–4000 g)	114 (67%)	75 (68%)	39 (65%)	
Large (LGA) (> 4000 g)	43 (25%)	26 (24%)	17 (28%)	
Fasting plasma glucose (mmol/l)	12.5 (7.6–16.7)	10.6 (7.6–14.8)	17.1 (7.7–18.5)	**0.021**
Fasting insulin level (μU/ml)	21.4 (11.96–40.2)	23.1 (16.4–46.2)	16.6 (11.1–44.7)	0.26
Fasting C-peptide (ng/ml)	3.5 (2.66–5.1)	3.4 (2.67–4.91)	4.2 (2.58–5.87)	0.20
HbA_{1c} (mmol/mol) (%)	84 (9.8) ± 5 (2.6)	80 (9.5) ± 1.6 (2.3)	91 (10.5) ± 9 (3)	**0.005**
Triglyceride ≥ 1.5 mmol/l	73 (53.7%) *n* = 136	63 (61.8%) *n* = 105	16 (55.2%) *n* = 31	0.333
LDL-cholesterol ≥ 3.4 mmol/l	96 (75%) *n* = 128	73 (75.3%) *n* = 97	23/31 (74.2%) *n* = 31	0.539
HDL-cholesterol < 1 mmol/l	65 (51.6%) *n* = 101	45 (47.9%) *n* = 61	20 (62.5%) *n* = 32	0.154

Age, BMI, BMI Z-score, HbA_{1C} expressed as mean (SD); fasting blood glucose, insulin, C-peptide levels as median (25th to 75th percentile); all others as percentages.
AGA, appropriate for gestational age; LGA, large for gestational age; SGA, small for gestational age. Data in bold are statistically significant.

between the gender groups for the age at diagnosis, pubertal status, the presence of acanthosis nigricans and diabetic symptoms. Female children were more likely to have higher BMI Z-scores (Table 2).

Findings at the time of diagnosis

The median fasting blood glucose was 12.5 mmol/l (7.6–16.7, range 4.2–44.5), the median insulin and C-peptide levels were 21.4 μU/ml (14.6–45.1, range 1.9–333) and 3.5 ng/ml (2.6–5.07, range 0.3–22.2), respectively. The mean HbA_{1C} level was 84 ± 5 mmol/mol (9.8 ± 2.6%) [range 48–178 mmol/mol (6.5–18%)]. HbA_{1C} levels of all children with fasting blood glucose < 7 mmol/l were ≥ 48 mmol/mol (6.5%). Only 11% of the children had ketoacidosis and/or ketonaemia at presentation. Measurement of diabetes-related autoantibodies were performed in 109 of the 227 children (48%), and all of those were negative. All of the remaining children who were not tested for diabetes-related autoantibodies had elevated C-peptide and/or insulin levels meeting the inclusion criteria. Only 99 of the 227 children had been assessed with respect to non-alcoholic fatty liver disease and 73 (73%) were shown to have hepatosteatosis. Dyslipidaemia and microalbuminuria were detected in 75 and 4.4%, respectively. The median plasma glucose and mean HbA_{1C} levels were significantly higher among male children at the time of diagnosis whereas serum insulin and C-peptide levels and the frequency of dyslipidaemia were comparable in both gender groups (Table 2).

When a total of 109 children who had negative-antibody tests were analysed separately, the median fasting blood glucose was 13.7 mmol/l (25th–75th percentiles = 8–17.8, range 4.9–43.7), the median insulin level and C-peptide levels were 21.4 μU/ml (25th–75th percentiles = 9.8–50.4, range 1.3–333) and 3.5 ng/ml (25th–75th percentiles = 2.6–5.09, range 0.61–22.2), respectively. The mean HbA_{1C} level was 88 ± 4.91 mmol/mol (10.2 ± 2.6%) [range 48–177.6 mmol/mol (6.5–18.4%)]. The significant difference associated with BMI-SDS, blood glucose and HbA_{1C} levels remained; median fasting insulin level was shown to be significantly higher in female children (Table 3).

Comparison of the clinical and biochemical findings at diagnosis in respect of pubertal status

Fourteen of the 227 children (6%) were younger than 10 years old at diagnosis. There was no statistical difference among children who were prepubertal (Tanner stage 1), mid-pubertal (Tanner stages 2–4) and late pubertal (Tanner stage 5) regarding fasting glucose, insulin, C-peptide and HbA_{1C} levels at diagnosis. Fasting triglyceride, LDL- and HDL-cholesterol levels were also comparable in the three groups. However, the mean age, BMI and BMI Z-scores, and the ratio of the presence of classical diabetes symptoms were significantly high in the late pubertal group (Table 4). All prepubertal children were autoantibody negative and no children had ketoacidosis or ketonaemia.

Treatment modalities

Only 13% (*n* = 29) of the children were treated solely with lifestyle modification, while 40.5% (*n* = 92) were treated with metformin, 13% (*n* = 30) were treated with insulin, and 33.5% (*n* = 76) were initially treated with a combination of insulin and metformin. The median age, proportion of prepubertal children, presence of acanthosis nigricans and

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Table 3 Clinical and laboratory features of the antibody negative cases by sex at diagnosis

	Overall (*N* = 109)	Female (*N* = 77)	Male (*N* =3 2)	*P*-value
Age (years)	14.1 ± 2.1 (range 6.5–17.8)	13.8 ± 2.1 (range 7.8–17.6)	14.6 ± 2 (range 6.5–17.8)	0.066
BMI (kg/m^2)	30.3 ± 5.6 (18.7–49.4)	30.3 ± 5.8 (20–49.4)	30.2 ± 5 (18.7–45.2)	0.93
BMI SD	2.2 ± 0.7 (1–4.6)	2.3 ± 0.7 (1.1–4.6)	2 ± 0.6 (1–3.3)	**0.016**
Prepubertal (Tanner stage 1)	4 (3.7%)	3 (3.9%)	1 (3.1%)	0.845
Presence of acanthosis nigricans	74 (68%)	50 (64%)	24 (75%)	0.305
Presence of diabetes symptoms	56 (51.4%)	35 (45.4%)	21 (65.6%)	0.062
Size at term birth	*n* = 89	*n* = 59	*n* = 30	0.492
Small (SGA) (< 2500 g)	9 (10.1%)	8 (13.6%)	1 (3.3%)	
Normal (AGA) (2500–4000 g)	59 (66.3%)	37 (62.7%)	22 (73.3%)	
Large (LGA) (> 4000 g)	21 (19.3%)	14 (23.7%)	7 (23.3%)	
Fasting blood glucose (mmol/L)	13.7 (8–17.8)	11.2 (7.8–16)	17.1 (12.2–18.9)	**0.009**
Fasting insulin level (μU/ml)	19.1 (9.8–50.4)	21.5 (14.1–51.9)	16 (6.2–36.9)	**0.047**
Fasting C-peptide (ng/ml)	3.5 (2.6–5.09)	3.4 (2.6–5.09)	4 (2.3–5.4)	0.569
HbA_{1c} (mmol/mol) (%)	88 ± 4.9 (10.2 ± 2.6) [range 48-178 (6.5–18.4)]	83 ± 4 (9.7 ± 2.5) [range 48–178 (6.5–18.4)]	100 ± 4.9 (11.3 ± 2.6) [range 51–158 (6.8–16.6)]	**0.04**
Triglyceride ≥ 1.5 mmol/l	30 (40%) *n* = 75	22(38.6%) *n* = 57	11 (61.1%) *n* = 18	0.661
LDL-cholesterol ≥ 3.4 mmol/l	58 (77.3%) *n* = 75	42(%75) *n*= 56	16(84.2%) *n* = 19	0.410
HDL-cholesterol < 1 mmol/l	34 (48.6%) *n* = 70	23 (44.2%) *n* = 52	11 (61.1%) *n* = 18	0.220

Age, BMI, BMI Z-score, HbA_{1C} expressed as mean (SD); fasting blood glucose, insulin, C-peptide levels as median (25th to 75th percentile); all others as percentages.
AGA, appropriate for gestational age; LGA, large for gestational age; SGA, small for gestational age. Data in bold are statistically significant.

serum C-peptide levels were comparable across treatment groups. The children who were treated with metformin alone were more likely to be female (79%) compared with those who were treated with a combination of metformin and insulin. Median BMI and BMI Z-scores were significantly lower in those children who were treated with a combination of insulin and metformin compared with those who were treated with metformin alone (P = 0.025 and P = 0.027, respectively). The children who were treated with metformin alone were less likely to have diabetes symptoms at diagnosis (P < 0.001). Fasting blood glucose and HbA_{1C} levels of children who were treated with insulin and combination of insulin and metformin were higher than those who were not treated with insulin (P < 0.001). Median fasting serum insulin level was higher in those treated solely with lifestyle modification compared with those treated with insulin alone or combination of metformin and insulin (P = 0.002) (Table 5).

Discussion

This is the first report from Turkey presenting the initial clinical and biochemical features of children diagnosed with Type 2 diabetes. The findings of this multicentre, cross-sectional study showed that the majority of children were identified through opportunistic screening of asymptomatic children and adolescents who were at high risk of Type 2 diabetes. The proportion of children who had typical diabetes symptoms at the time of diagnosis was only 43%. Participants in more recent studies were more likely to be asymptomatic at the time of diagnosis compared with previous studies from the USA. Accordingly, this proportion was 67% in the Pediatric Diabetes Consortium (PDC) report [17]. The ratio of asymptomatic cases was stated as 33% in non-Caucasian vs. 50% in Caucasian populations [8]. The results of various studies underline the necessity of screening of high-risk children for Type 2 diabetes. The American Diabetes Association has already recommended screening overweight and obese children with at least two additional risk factors, starting at age 10 or at the onset of puberty if it begins earlier [12]. The age limit of 10 years is based on onset of puberty and physiological insulin resistance during puberty [18].

However, in recent years, young children aged < 10 years have been reported as having Type 2 diabetes. Indeed, 8% of the PDC Type 2 diabetes cohort consisting of individuals aged < 21 years diagnosed with Type 2 diabetes were aged < 10 years at the time of diagnosis [17]. This ratio was 6% in our study and comparable with the PDC cohort. Interestingly, the majority (10 of 14 children) of the younger group was prepubertal. Despite the rarity of Type 2 diabetes among prepubertal children, 20 children diagnosed with Type 2 diabetes aged < 10 years were recently reported at a single centre in the USA and one patient from this cohort was aged 5 years at the time of diagnosis [19]. Although the increasing frequency of obesity and insulin resistance among young children can explain the development of Type 2 diabetes even in prepubertal children, the probability of inaccurate

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Table 4 Clinical and laboratory characteristics of participants by pubertal status

	Prepubertal (Tanner stage 1) (n = 15)	Mid-pubertal (Tanner stage 2–4) (n = 78)	Late pubertal (Tanner stage 5) (n = 134)	P-value
Age (years)	9.1 (8.5–10.4)	13.1 (11.8–14.2)	14.9 (13.7–15.8)	< 0.001*
BMI (kg/m^2)	26 (23.5–30.9)	28.2 (25.3–35)	31.9 (28.2–35)	< 0.001†
BMI-SDS	2.3 (1.8–3.3)	2.1 (1.7–2.6)	2.4 (1.9–3.7)	0.02‡
Presence of acanthosis nigricans	8 (53.3%)	48 (61.5%)	101 (75.3%)	0.04
Presence of diabetes symptoms	8 (53.3%)	42 (53.8%)	47 (35%)	0.02§
Fasting plasma glucose (mmol/l)	8.9 (7.6–23.8)	14.1 (7.4–20)	12.2 (9–16.8)	0.911
Fasting insulin level (μU/ml)	23.3 (18.9–32.3)	18.9 (8.9–34.9)	25.1 (13–44.5)	0.638
Fasting C-peptide (ng/ml)	3.82 (3.2–4.8)	3.51 (2.7–4.7)	3.49 (2.6–5.6)	0.762
HbA_{1c} (mmol/mol) (%)	50 (6.7) [range 48–66 (6.5–8.2)]	73 (8.8) [range 55–101 (7.2–11.4)]	77 (9.2) [range 63–99 (7.9–11.2)]	0.737
Triglyceride (mmol/l)	2 (1.3–2.3)	1.8 (1.3–2.6)	1.6 (1.2–2.5)	0.198
LDL-cholesterol (mmol/l)	2.7 (2.5–3.2)	2.7 (2.3–3.5)	2.9 (2.2–3.3)	0.954
HDL-cholesterol (mmol/l)	0.9 (0.8–1.3)	1 (0.8–1.1)	1 (0.9–1.2)	0.691

Age, BMI, BMI Z-score, HbA_{1C} expressed as mean (SD); fasting blood glucose, insulin, C-peptide levels as median (25th to 75th percentile); all others as percentages.
Significant post-hoc comparisons:
*between all groups ($P < 0.0125$).
†late pubertal group vs. prepubertal group and mid-pubertal group ($P < 0.0125$).
‡late pubertal group vs. mid-pubertal group ($P < 0.0125$).
§late pubertal group vs. mid-pubertal group ($P < 0.0125$).

classification of diabetes in young children should not be ignored. Accordingly, almost 20% of children who were excluded from our study because they did not meet the diagnostic criteria for Type 2 diabetes were aged < 10 years. The accurate diagnosis of Type 2 diabetes in youth might be very difficult because of transient alterations in C-peptide levels and insulin secretion as well as antibody positivity [20,21]. Furthermore, with increasing obesity in childhood, as many as 30% of children newly diagnosed with Type 1 diabetes or monogenic diabetes may be obese, depending on the rate of obesity in the background population. Furthermore, a significant number of children diagnosed with Type 2 diabetes demonstrate ketonuria or ketoacidosis at diagnosis. [22,23]. The positivity of antibodies is not rare (21.5% in

Table 5 Clinical and biochemical features of participants by different treatment modalities

	Lifestyle modification alone (N = 29)	Metformin (N = 92)	Insulin (N = 30)	Metformin+ insulin (N = 76)	P-value
Age (years)	13.7 (12.1–14.9)	14.1 (12.7–15.6)	14.1 (12.4–14.9)	14.4 (13–15.4)	0.27
Female (%)	59 (n = 17)	79 (n = 73)	67 (n = 20)	59 (n = 45)	0.025*
BMI (kg/m^2)	31.1 (29.2–33.4)	29.2 (26.1–34.4)	30.2 (27.7–33.7)	27.7 (25.1–33.5)	0.027†
BMI SD	2.3 (2.1–2.8)	2.5 (1.9–2.9)	2.2 (1.7–2.4)	1.9 (1.5–2.5)	< 0.001‡
Tanner stage 1	4 (14%)	7 (8%)	1 (3%)	3 (4%)	0.267
Presence of acanthosis nigricans	18 (62%)	66 (72%)	19 (63%)	54 (71%	0.66
Presence of diabetes symptoms	15 (52%)	21 (23%)	15 (50%)	46 (60%)	< 0.001§
Fasting blood glucose (mmol/l)	8.2 (6.9–10.4)	8.6 (7.3–11.7)	16 (11–21.7)	16.7 (12.8–21.4)	< 0.001¶
HbA_{1c} (mmol/mol) (%)	70 (8.6) (56–97 (7.3–11))	67 (8.3) (56–85 (7.3–9.9))	98 (11.1) (83–128 (9.7–13.9))	102 (11.5) (86–120 (10–13.1))	< 0.001¶
Fasting insulin (μU/ml)	28 (15.5–52)	25.4 (17.3–55.7)	18.1 (12.2–31.8)	16.3 (7.1–37.8)	0.002¶
Fasting C-peptide (ng/ml)	3.8 (3.4–6.3)	3.86 (2.7–5.6)	3.4 (2.6–4.6)	3.4 (2.1–4.5)	0.134

Age, BMI, BMI Z-score, HbA_{1C} expressed as mean (SD); fasting blood glucose, insulin, C-peptide levels as median (25th to 75th percentile); all others as percentages.
Significant post-hoc comparisons:
*Metformin group vs. metformin + insulin group ($P = 0.004$).
†Metformin group vs. metformin + insulin group ($P = 0.006$).
‡Metformin group vs. metformin + insulin group ($P < 0.001$), metformin + insulin group vs. lifestyle modification alone group ($P = 0.001$).
§Metformin + insulin vs. metformin group ($P < 0.001$), lifestyle modification alone group vs. metformin group ($P < 0.001$).
¶Insulin group vs. lifestyle modification alone group ($P < 0.001$), metformin + insulin group vs. metformin group, metformin group vs. insulin group ($P < 0.001$).

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the SEARCH data) among children with Type 2 diabetes [21]. Whether these children have both autoimmune Type 1 diabetes and Type 2 diabetes or if they are obese children with Type 1 diabetes is unclear. Results of the TODAY study showed that C-peptide levels of antibody-positive Type 2 diabetes cases were lower compared with antibody-negative Type 2 diabetes cases but higher than classic Type 1 diabetes cases [24]. A couple of years ago, Tfayli *et al*. also showed that obese youth with a clinical diagnosis of Type 2 diabetes had evidence of islet cell autoimmunity with positive autoantibodies and had severe insulin deficiency and β-cell failure [25].

A specific predisposing factor for Type 2 diabetes has not been identified among Turkish children with Type 2 diabetes in this study. However, it was reported that children who had a positive family history of Type 2 diabetes were at increased risk of insulin resistance and prediabetes [26]. It can be implied that in Turkey the most important risk factor for Type 2 diabetes among children is positive family history. Indeed, the rate of positive family history was 86% in the current study and comparable with both PDC [15] and TODAY [24] cohorts (92 and 89.4%, respectively). Additionally, the WHO European Childhood Obesity Surveillance Initiative – COSI-Turkey indicated that from 2013 to 2016 the frequency of obesity and overweight among children aged 6–9 years increased from 8.3 to 9.9% and from 14.2 to 14.9%, respectively, suggesting an increased risk for Type 2 diabetes [27].

To date, a female preponderance has been shown in all paediatric Type 2 diabetes cohorts [17,28,29]. The majority (68%) of children in the current study were also female. BMI Z-scores were higher for female children. On the contrary, median blood glucose level and mean HbA_{1C} were significantly higher in male children. Gender-related differences were searched for in the TODAY cohort, however, no difference regarding BMI Z-scores was found [28]. A higher HbA_{1C} in male compared with female children and adolescents has not been reported to date. The gender-associated differences are not clear in the paediatric group and larger cohorts are needed to clarify these findings.

ISPAD guidelines recommend metformin monotherapy if the individual is metabolically stable (HbA_{1C} < 9% and without symptoms). Insulin treatment is recommended if the individual is not metabolically stable [11]. In the current study, the proportion of children treated solely with lifestyle modification was low (13%). Almost half of the children (46.5%) were started on insulin treatment at the time of diagnosis and 40.5% were started on metformin alone. The high rate of medical therapy was similar to the other paediatric cohorts in the USA [27] and Europe (85 and 86%, respectively) [29]. Fasting blood glucose and HbA_{1C} levels of children who were treated with insulin or a combination of insulin and metformin were significantly higher than those who were not treated with insulin, suggesting that physicians mostly follow International Society for Pediatric and Adolescent Diabetes (ISPAD) guidelines for the treatment of Type 2 diabetes.

The screening of lipid levels is crucial for early detection and for reducing diabetes-associated complications in youth with Type 2 diabetes [18]. In the present study, co-morbidities such as dyslipidaemia and microalbuminuria were found in 75 and 4.4% of children, respectively. The rate of dyslipidaemia was higher than the UK cohort (9%) but comparable with the TODAY cohort (80.5%), whereas the rate of microalbuminuria was similar to the UK cohort (3%) but lower than the TODAY cohort (13%) [28,30].

There were limitations to our study. The frequency of autoantibody testing was low, OGTT results were missing, and follow-up data were not available. We feel that this multicentre study is important as it is the first report representing the largest national sample of Turkish youth with recent-onset Type 2 diabetes. In conclusion, an opportunistic screening of children who are at high risk of Type 2 diabetes is essential as our data showed a substantial number of children were asymptomatic at diagnosis. The other important result of our study was the high exclusion rate, suggesting that different criteria are used to diagnose Type 2 diabetes in youth by paediatric endocrinologists. Large-scale studies with long-term follow-up are required to define the prominent features of Type 2 diabetes in children, particularly in those aged < 10 years. The overlap between Type 1 and Type 2 diabetes in children, with respect to phenotype and metabolic parameters, including pancreatic autoantibody positivity, contributes to the difficulty of classification at onset. Careful management based on metabolic characteristics is essential. Future studies will be expected to provide more insight into the natural history of autoantibody-negative Type 2 diabetes and intermediate cases in children and adolescents.

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Competing inetrests

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Ethical Approval

The study was approved by the Medical Ethics Committee of [INSTITUTION], and informed consent was obtained from all participants. This research study was conducted in accordance with the guidelines of the Declaration of Helsinki.

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