

Metformin treatment in pediatric obesity: A real-world experience showing pronounced 6-month improvement but limited long-term sustainability

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ABSTRACT

Objective: Metformin is widely used in pediatric obesity to improve insulin resistance. This study aimed to examine the association between metformin use and metabolic outcomes in adolescents with obesity, applying longitudinal follow-up and oral glucose tolerance test (OGTT)-based analyses to address this question.

Materials and Methods: Ninety-six adolescents with obesity (32 metformin-treated, 64 receiving lifestyle modification alone) were evaluated at baseline, 6 months, and 12 months. Anthropometric, biochemical, and OGTT-derived glucose and insulin parameters were analyzed.

Results: At baseline, the metformin group had significantly higher BMI ($p=0.005$), fasting insulin ($p=0.007$), HOMA-IR ($p=0.002$), HbA1c ($p<0.001$) and uric acid ($p=0.008$), indicating greater metabolic severity. OGTT analysis demonstrated comparable glucose levels but markedly elevated insulin responses across all time points in the metformin group, consistent with a hyperinsulinemic state. Both groups showed significant improvement in anthropometric and metabolic parameters at 6 months; however, partial deterioration was observed at 12 months. In adjusted analyses, metformin use remained associated with higher fasting insulin ($p=0.004$) and HOMA-IR ($p=0.003$) at 6 months, but not at 12 months ($p=0.080$ and $p=0.070$, respectively). Among patients not receiving metformin, elevated OGTT 1-hour glucose (>155 mg/dL) demonstrated a borderline association with higher BMI at 6 months ($p=0.078$).

Conclusion: In this observational cohort, adolescents treated with metformin represented a more severe metabolic phenotype at baseline. Although early (6-month) improvements were evident in both groups, these effects were not sustained at 12 months. No significant association was observed between metformin use and independent alteration of long-term metabolic trajectory beyond lifestyle modification alone. These findings suggest that metformin prescription reflects baseline disease severity; however, the observational design precludes definitive conclusions regarding treatment efficacy, and prospective randomized studies are needed.

Keywords: Hyperinsulinemia, insulin resistance, metabolic syndrome, metformin, OGTT, pediatric obesity

Introduction

Childhood and adolescent obesity has emerged as one of the most critical global health challenges of the 21st century, with a rapidly increasing prevalence and profound implications for long-term cardiometabolic health (1,2). Excess adiposity in early life is strongly associated with insulin resistance, which represents a central pathophysiological mechanism linking obesity to the development of type 2 diabetes mellitus (T2DM), dyslipidemia, nonalcoholic fatty liver disease (NAFLD), and premature cardiovascular disease (3). Importantly, insulin resistance may be present even in the absence of overt hyperglycemia, particularly in pediatric populations, where compensatory hyperinsulinemia often maintains normoglycemia for extended periods (2,4).

In children with obesity, the foundation of treatment is still lifestyle change working with the child and family on healthier eating habits, increasing daily physical activity, and supporting behavior changes through ongoing guidance and family involvement (5,6). Metformin is widely used in pediatric endocrinology as an insulin-sensitizing drug. Although originally developed for the treatment of T2DM, its use has expanded to include obesity-related insulin resistance, impaired glucose tolerance (IGT), and polycystic ovary syndrome (PCOS) in adolescents. The primary mechanisms of metformin include inhibition of hepatic gluconeogenesis, enhancement of peripheral glucose uptake, and improvement of insulin sensitivity, making it a rational therapeutic option for metabolic dysfunction associated with obesity (7,8).

A substantial body of literature has reported favorable effects of metformin in children and adolescents with obesity, including reductions in BMI, improvements in fasting insulin levels and HOMA-IR, and beneficial changes in lipid profiles. Some studies have also demonstrated modest improvements in glycemic parameters, including HbA1c (9-11). However, these findings are not entirely consistent across studies, and the magnitude and durability of these effects remain subjects of ongoing debate.

One of the major challenges in interpreting these findings lies in the inherent limitations of real-world clinical data. In routine practice, metformin is typically prescribed to patients with more pronounced metabolic abnormalities (12,13). This phenomenon, known as confounding by indication, complicates the interpretation of observational studies, as baseline differences in disease severity may account for apparent differences in outcomes rather than treatment effects. Another important gap in the literature relates to the evaluation of dynamic metabolic responses. While fasting measures such as glucose and insulin are widely used, they provide limited insight into the complex physiology of glucose metabolism. OGTT-derived indices, including time dependent glucose and insulin responses, offer a more comprehensive assessment of insulin sensitivity and β -cell function. Despite this, relatively few pediatric studies have incorporated detailed OGTT-based analyses.

Furthermore, the longitudinal sustainability of metabolic improvements with metformin remains uncertain. While short-term benefits are frequently reported, longer-term data suggest that these improvements may attenuate over time, particularly in the absence of sustained lifestyle modifications. Real-world studies have also demonstrated that treatment effects observed in controlled clinical trials may be less pronounced in routine clinical practice (14,15).

Taken together, these considerations highlight the need for comprehensive real-world analyses that integrate baseline severity, longitudinal changes, dynamic metabolic testing, and sex-specific effects. The primary objective of this study was to examine the association between metformin use and anthropometric, biochemical, and dynamic metabolic parameters in adolescents with obesity in a real-world clinical setting. Secondary objectives included evaluating longitudinal changes in metabolic parameters at baseline, 6 months, and 12 months within each group, and assessing insulin resistance using both fasting indices (HOMA-IR) and OGTT-derived measures, with particular emphasis on the discriminative value of a 1-hour OGTT glucose level >155 mg/dL.

Materials and Methods

Study design and population

This retrospective cohort study included 96 adolescents with obesity followed in our pediatric endocrinology clinic between January 2021 and January 2026. Adolescents aged 10–18 years with available data at baseline, 6-month, and 12-month follow-up visits were included. Lifestyle modification was recommended to all participants. Patients were stratified into two groups based on metformin use at

baseline: the metformin group (n=32) and the non-metformin group (n=64).

Patient flow: A total of 142 adolescents with obesity were initially screened for eligibility. Of these, 46 were excluded for the following reasons: 18 had incomplete follow-up data (missing 6-month or 12-month visits), 14 had obesity secondary to identifiable causes (5 with genetic syndromes, 4 with medication-induced obesity, 3 with hypothalamic obesity, 2 with Cushing syndrome), 8 had incomplete metabolic measurements (missing OGTT or key laboratory parameters), and 6 had chronic diseases affecting metabolic parameters (chronic kidney disease, inflammatory bowel disease). The final analytic cohort comprised 96 adolescents with obesity who met all inclusion criteria and had complete longitudinal data at all three time points.

Patients with obesity due to causes other than exogenous obesity such as chronic diseases, monogenic obesity, medication-related obesity, or eating disorders were excluded. Additionally, individuals with incomplete follow-up data or missing metabolic measurements were not included in the analysis.

OGTT procedure

All patients underwent a standard OGTT at baseline following an overnight fast of at least 8 hours. Patients were instructed to maintain their usual diet for at least 3 days prior to the test and to avoid vigorous physical activity on the evening before and morning of the test. The test was performed in the morning (between 8:00 and 10:00 AM) with the patient in a seated position. After collection of a fasting blood sample (time 0), patients ingested a glucose solution containing 1.75 g of glucose per kilogram of body weight (maximum 75 g) within 5 minutes. Venous blood samples were then collected at 30, 60, 90, and 120 minutes after glucose ingestion. At each time point, plasma glucose and serum insulin levels were measured. Patients remained seated and at rest throughout the test and were not permitted to eat or drink (except water) during the 2-hour procedure.

Plasma glucose was measured using the hexokinase enzymatic method, and serum insulin was measured using a chemiluminescent immunoassay. Total insulin exposure was calculated as the area under the curve (AUC), and mean insulin was calculated as total insulin divided by the number of time points.

Metformin treatment protocol

Metformin was prescribed at the discretion of the treating pediatric endocrinologist based on clinical judgment, typically in adolescents with obesity presenting with marked insulin resistance (HOMA-IR >4.0), impaired fasting glucose (IFG), IGT, or HbA1c in the prediabetic range (5.7–6.4%). The decision to initiate metformin was individualized and took into account the severity of metabolic derangement, family history of T2DM, and clinical features of insulin resistance.

The typical starting dose was 500 mg once daily, administered with the evening meal to minimize gastrointestinal side effects. The dose was titrated upward by 500 mg increments at 1-to 2-week intervals as tolerated, with a target maintenance dose of 1000–2000 mg daily, divided into two

doses (morning and evening).

Medication adherence was assessed through patient and parent self-report at each follow-up visit, with adherence categorized as good (>80% of prescribed doses taken), moderate (50–80%), or poor (<50%).

Lifestyle intervention

All participants, regardless of metformin use, received standardized lifestyle modification counseling as the foundation of treatment. The lifestyle intervention was delivered by a multidisciplinary team consisting of a pediatric endocrinologist, a registered dietitian, and a clinical psychologist specializing in pediatric obesity.

Dietary counseling: Patients and their families received individualized dietary counseling at baseline and at each follow-up visit (6 and 12 months). The dietitian provided education on healthy eating patterns, portion control, reduction of sugar-sweetened beverages and high-calorie snacks, and increased consumption of fruits, vegetables, and whole grains. Specific caloric targets were not prescribed; instead, the focus was on qualitative dietary improvements and family-based behavioral strategies. Families were encouraged to implement structured meal times, reduce screen time during meals, and involve the child in meal planning and preparation.

Physical activity recommendations: All participants were counseled to engage in at least 60 minutes of moderate-to-vigorous physical activity daily, in accordance with World Health Organization guidelines for children and adolescents. Recommendations included a combination of aerobic activities (walking, cycling, swimming, sports) and muscle-strengthening exercises. Families were encouraged to reduce sedentary behaviors, particularly recreational screen time, to less than 2 hours per day.

Behavioral support and family involvement: Behavioral counseling emphasized goal-setting, self-monitoring, and problem-solving strategies to support sustainable lifestyle changes. Parents and caregivers were actively involved in all counseling sessions, as family-based interventions have been shown to be most effective in pediatric obesity. The clinical psychologist provided additional support for families facing barriers to adherence, including motivational interviewing and cognitive-behavioral techniques.

Adherence assessment: Adherence to lifestyle recommendations was assessed qualitatively through patient and parent self-report at each follow-up visit. Families were asked to describe changes in dietary habits, physical activity levels, and screen time. However, objective measures of adherence (e.g., food diaries, accelerometry) were not systematically collected in this real-world clinical cohort. The intensity and frequency of lifestyle counseling were comparable between the metformin and non-metformin groups; however, individual variability in adherence and engagement likely contributed to heterogeneity in outcomes.

Clinical and laboratory assessments

Clinical, anthropometric, and laboratory data were collected at three time points: baseline (initial visit), 6 months, and 12

months. The following parameters were recorded at each visit:

Anthropometric measurements: Body weight (kg) and height (cm) were measured using a calibrated stadiometer and scale. BMI was calculated as weight in kilograms divided by height in meters squared (kg/m^2). BMI standard deviation score (BMI SDS) was calculated using age- and sex-specific reference data.

Biochemical parameters: Fasting blood samples were obtained at each visit after an overnight fast of at least 8 hours. The following parameters were measured: fasting glucose (FG), fasting insulin, HbA1c, lipid profile (total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), very low-density lipoprotein cholesterol (VLDL-C)), hepatic enzymes (aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT)), and uric acid. HOMA-IR was calculated using the formula: $(\text{fasting glucose (mg/dL)} \times \text{fasting insulin (}\mu\text{IU/mL)}) / 405$.

Blood pressure: Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured three times after 10 minutes of rest in the supine position using an automated oscillometric device with an appropriately sized cuff. The mean of the three measurements was calculated and recorded.

Diagnostic criteria and definitions

Obesity: Obesity was diagnosed in patients with a BMI greater than the 95th percentile for age and sex according to the Centers for Disease Control and Prevention (CDC) growth charts (16).

Screening indications: In accordance with the International Society for Pediatric and Adolescent Diabetes (ISPAD) Clinical Practice Consensus Guidelines, adolescents with a BMI ≥ 85 th percentile were screened for T2DM, dyslipidemia, and hypertension. Screening was recommended in the presence of at least one additional risk factor, including a family history of T2DM, high-risk ethnic background, clinical features of insulin resistance (acanthosis nigricans, PCOS), abnormal birth weight (small or large for gestational age), or maternal diabetes, including gestational diabetes (17).

Hypertension: SBP and DBP were classified based on the National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents (2004) guidelines (18).

Glucose tolerance classification: According to the American Diabetes Association (ADA) criteria, glucose tolerance was classified as follows: FG <100 mg/dL and 2-hour plasma glucose (2-h PG) <140 mg/dL indicate normal glucose tolerance; FG 100–125 mg/dL defines IFG; 2-h PG 140–199 mg/dL defines IGT; and FG ≥ 126 mg/dL and/or 2-h PG ≥ 200 mg/dL is diagnostic of diabetes mellitus (19).

Metabolic syndrome: Metabolic syndrome was defined according to age-specific criteria (20).

OGTT 1-Hour Glucose Threshold: Patients were further stratified according to 1-hour OGTT glucose levels (≤ 155 mg/dL vs. >155 mg/dL), as this threshold has been shown to identify adolescents at higher risk for future T2DM (21).

Statistical analysis

All analyses were performed using SPSS version 22.0 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean and standard deviation (SD) for normally distributed data and median (IQR) for non-normally distributed data. Categorical variables were presented as frequencies and percentages.

Baseline differences between metformin and non-metformin groups were analyzed using independent samples t-test or Mann–Whitney U test for continuous variables and chi-square test for categorical variables. A univariable binary logistic regression analysis was performed to evaluate the association between metformin use (independent variable) and a 1-hour OGTT glucose level ≥ 155 mg/dL (dependent variable). No additional covariates were included in the model. Results were expressed as unadjusted odds ratios (ORs) with 95% confidence intervals (CIs). Changes over time (baseline, 6 months, 12 months) within each group were evaluated using repeated-measures analysis of variance (ANOVA) or Friedman test, as appropriate. (i) The primary analysis was ANCOVA, with 6 and 12 month outcomes adjusted for baseline values, age, and sex; (ii) since measurements at all three time points were available for all patients, the linear mixed-effects model was used only as a complementary/ sensitivity analysis to test the group $\times$ time interaction (i.e., whether the metabolic trajectory differed between groups); (iii) repeated-measures ANOVA/Friedman tests were applied only to describe within-group changes over time and were supported by post-hoc pairwise comparisons (Bonferroni). A p-value < 0.050 was considered statistically significant.

Results

Baseline characteristics

A total of 96 adolescents with obesity were included in the analysis, of whom 32 (33.3%) were prescribed metformin at baseline and 64 (66.7%) received lifestyle modification alone (Table I). The metformin group exhibited significantly higher body weight (102.45 kg (95.00–112.50) vs. 88.40 kg (83.00–98.10), $p < 0.001$), BMI (35.80 kg/m² (32.80–40.44) vs. 32.80 kg/m² (31.10–34.80), $p = 0.005$), and BMI SDS (3.32 (2.58–3.91) vs. 2.78 (2.49–3.20), $p = 0.005$) compared to the non-metformin group. In the present cohort, the median maintenance dose was 1500 mg/day (interquartile range (IQR) 1000–2000 mg/day).

Metabolic parameters were also more adverse in the metformin group, with significantly elevated FG (93.0 mg/dL (86.0–97.5) vs. 91.0 mg/dL (84.0–94.25), $p = 0.040$), fasting insulin (29.0 μ U/mL (21.75–37.25) vs. 19.5 μ U/mL (15.0–29.0), $p = 0.007$), HOMA-IR (7.2 (4.8–9.5) vs. 4.3 (2.7–6.0), $p = 0.002$), HbA1c (5.90 $\pm$ 0.4% vs. 5.45 $\pm$ 0.3%, $p < 0.001$), and uric acid (6.9 $\pm$ 1.3 mg/dL vs. 5.8 $\pm$ 1.2 mg/dL, $p = 0.008$). No significant differences were observed in age, SBP, or DBP between groups.

Baseline OGTT findings

Baseline OGTT glucose values were compared between groups using the Mann–Whitney U test and are presented as median (IQR). The metformin group demonstrated higher

Table I: Baseline demographic, anthropometric, and biochemical characteristics by metformin status

	Metformin	No Metformin	p
Total number of patients	32	64	-
Age (years)*	15.2 $\pm$ 1.6	14.8 $\pm$ 1.9	0.280
Sex (Female/Male) †	19/13	36/28	0.720
Body weight (kg)‡	102.45 (95.00–112.50)	88.40 (83.00–98.10)	< 0.001
BMI (kg/m ²)‡	35.80 (32.80–40.44)	32.80 (31.10–34.80)	0.005
BMI SDS‡	3.32 (2.58–3.91)	2.78 (2.49–3.20)	0.005
Fasting glucose (mg/dL)‡	93.0 (86.0–97.5)	91.0 (84.0–94.25)	0.040
Fasting insulin (μ U/mL)‡	29.0 (21.75–37.25)	19.5 (15.0–29.0)	0.007
HOMA-IR‡	7.2 (4.8–9.5)	4.3 (2.7–6.0)	0.002
HbA1c (%)*	5.90 $\pm$ 0.4	5.45 $\pm$ 0.3	< 0.001
Uric acid (mg/dL)*	6.9 $\pm$ 1.3	5.8 $\pm$ 1.2	0.008
Systolic blood pressure (mmHg)*	120.00 (120.00–134.75)	120.00 (117.00–130.00)	0.134
Diastolic blood pressure (mmHg)*	71.00 (69.75–80.00)	70.00 (60.00–80.00)	0.093

*: mean $\pm$ SD (Independent samples t-test), †: ratio, ‡: median (IQR) (Mann–Whitney U test), **BMI**: body mass index, **SDS**: standard deviation score, **HOMA-IR**: homeostasis model assessment of insulin resistance

FG, 60-minute glucose ($p = 0.040$) and 120-minute glucose ($p = 0.050$) compared to the non-metformin group. No significant differences were observed in 30-minute ($p = 0.347$) or 90-minute glucose values ($p = 0.40$).

Longitudinal changes within groups

Both groups demonstrated significant within-group changes over the 12-month follow-up period (Table II). In the metformin group, a significant overall change over time was observed in body weight ($p = 0.003$), BMI (36.4, 35.1, and 35.6 kg/m² at baseline, month 6, and month 12, respectively; $p = 0.022$), and BMI SDS (3.40, 3.15, and 3.25; $p = 0.011$). However, none of the Bonferroni-adjusted pairwise comparisons reached statistical significance for body weight (baseline–month 6, $p = 0.255$; baseline–month 12, $p = 1.000$; month 6–month 12, $p = 0.312$), BMI ($p = 0.639$, $p = 1.000$, and $p = 1.000$, respectively), or BMI SDS ($p = 0.536$, $p = 0.228$, and $p = 0.729$, respectively). HbA1c (5.90%, 5.60%, and 5.75%; $p < 0.001$), uric acid (6.9, 6.2, and 6.7 mg/dL; $p < 0.001$), ALT ($p = 0.011$), and HOMA-IR (4.3, 3.5, and 4.0; $p = 0.001$) also changed significantly over time. In post-hoc comparisons, HbA1c was significantly lower at both month 6 ($p < 0.001$) and month 12 ($p < 0.001$) than at baseline, with no significant difference between month 6 and month 12 ($p = 0.316$). Uric acid was significantly lower at month 6 than at baseline ($p = 0.008$) and increased significantly between month 6 and month 12 ($p < 0.001$), with no significant difference between baseline and month 12 ($p = 0.082$). ALT differed significantly only between baseline and month 6 ($p = 0.047$), whereas the baseline–month 12 ($p = 1.000$) and month 6–month 12 ($p = 0.059$) comparisons were not significant.

In the non-metformin group, significant changes over time were also observed. Body weight differed significantly in all pairwise comparisons (baseline–month 6, $p = 0.021$; baseline–

Table II: Within-group longitudinal changes in key metabolic parameters at baseline, 6 months, and 12 months

	Baseline	6 months	12 months	p
Body weight (kg)				
Metformin*	104.1	101.8	102.9	0.003
No metformin†	89.7	86.9	88.8	<0.001
BMI (kg/m ²)†				
Metformin	36.4	35.1	35.6	0.022
No metformin	32.9	31.8	33.2	<0.001
BMI SDS				
Metformin	3.40	3.15	3.25	0.011
No metformin†	2.80	2.65	2.90	<0.001
Fasting insulin (μIU/mL)†				
Metformin	30.5	25.2	27.0	0.430
No metformin	19.0	15.8	18.3	<0.001
HOMA-IR†				
Metformin	7.2	5.9	6.5	0.370
No metformin	4.3	3.5	4.0	0.001
HbA1c (%)†				
Metformin	5.90	5.60	5.75	<0.001
No metformin	5.45	5.28	5.38	<0.001
Uric acid (mg/dL)				
Metformin*	6.9	6.2	6.7	<0.001
No metformin†	5.8	5.4	5.9	<0.001
ALT (U/L)†				
Metformin	42.5	34.2	39.1	0.011
No metformin	36.8	29.5	32.7	0.016
AST (U/L)†				
Metformin	28.4	26.9	27.8	0.380
No metformin	26.7	23.4	24.8	0.036
GGT (U/L)†				
Metformin	31.2	29.8	30.6	0.115
No metformin	28.5	24.1	26.3	0.017
Total cholesterol				
Metformin†	182.4	178.9	181.7	0.552
No metformin*	176.2	168.5	171.9	0.021
Triglycerides†				
Metformin	148.7	139.5	144.8	0.223
No metformin	136.4	120.2	128.6	<0.001
LDL cholesterol				
Metformin†	109.3	106.8	108.7	0.999
No metformin*	104.5	96.3	99.8	<0.001
HDL cholesterol (mg/dL)†				
Metformin	42.1	44.5	43.2	0.096
No metformin	43.8	46.9	45.1	0.018
VLDL cholesterol (mg/dL)†				
Metformin	29.7	27.9	28.8	0.991
No metformin	27.3	24.0	25.7	0.002

*: Mean (Repeated-measures ANOVA), †: Median (Friedman test) **BMI**: body mass index, **HOMA-IR**: homeostatic model assessment of insulin resistance, **HbA1c**: glycated hemoglobin, **ALT**: alanine aminotransferase, **AST**: aspartate aminotransferase, **GGT**: gamma-glutamyl transferase, **LDL**: low-density lipoprotein, **HDL**: high-density lipoprotein, **VLDL**: very-low-density lipoprotein.

month 12, $p=0.036$; month 6–month 12, $p<0.001$). BMI differed significantly between baseline and month 6 ($p<0.001$) and between month 6 and month 12 ($p=0.021$), but not between baseline and month 12 ($p=1.000$), while none of the pairwise comparisons for BMI SDS were significant ($p=0.062$, $p=1.000$, and $p=0.192$, respectively). HbA1c (5.45%, 5.28%, and 5.38%; $p<0.001$) differed significantly between baseline and month 6 ($p=0.033$) and between month 6 and month 12 ($p<0.001$), with no significant difference between baseline and month 12

Table III: Adjusted between-group comparisons at 6 and 12 months (ANCOVA)

Outcome	Time Point	Adjusted Effect (Metformin vs No Metformin)	95% CI	p
BMI	6 months	+0.48 kg/m ²	−0.42–1.38	0.290
BMI	12 months	+0.62 kg/m ²	−0.50–1.75	0.270
Fasting insulin	6 months	Ratio 1.410	1.032–2.361	0.004
Fasting insulin	12 months	Ratio 1.18	0.96–1.44	0.080
HOMA-IR	6 months	Ratio 1.477	1.066–2.439	0.003
HOMA-IR	12 months	Ratio 1.20	0.97–1.46	0.070
Uric acid	6 months	+0.235 mg/dL	−0.388– +0.859	0.459
Uric acid	12 months	+0.728 mg/dL	0.040–1.199	0.037

ANCOVA models adjusted for baseline value, age, and sex. NS, not significant.

($p=1.000$). Uric acid (5.8, 5.4, and 5.9 mg/dL; $p<0.001$) differed significantly in all pairwise comparisons ($p<0.001$, $p=0.006$, and $p<0.001$, respectively). For ALT, a significant difference was found only between month 6 and month 12 ($p=0.048$), not between baseline and month 6 ($p=0.997$) or baseline and month 12 ($p=0.882$). Changes in other hepatic enzymes and lipid parameters are presented in Table II.

Between-Group comparisons after adjustment for baseline covariates

After adjusting for baseline values, age, and sex using ANCOVA, no significant between-group differences in BMI were observed at either 6 months (adjusted difference +0.48 kg/m², 95% confidence interval (CI) −0.42 to 1.38, $p=0.29$) or 12 months (adjusted difference +0.62 kg/m², 95% CI −0.50 to 1.75, $p=0.270$) (Table III).

Insulin resistance markers remained significantly elevated in the metformin group at 6 months: fasting insulin was 1.410-fold higher (95% CI 1.032–2.361, $p=0.004$) and HOMA-IR was 1.477-fold higher (95% CI 1.066–2.439, $p=0.003$). By 12 months, these differences were no longer statistically significant. No significant adjusted difference was observed in uric acid between groups at 6 months (adjusted difference +0.235 mg/dL, 95% CI −0.388 to +0.859, $p=0.459$). At 12 months, uric acid remained significantly elevated in the metformin group (adjusted difference +0.728 mg/dL, 95% CI 0.040–1.199, $p=0.037$).

Mixed-Effects model analysis

Adjusted BMI did not differ significantly between the metformin and non-metformin groups among females at 6 months (adjusted difference=+0.14 kg/m², 95% CI −1.24 to 1.52, $p=0.837$) or 12 months (+0.59 kg/m², 95% CI −1.73 to 2.91, $p=0.612$), nor among males (6 months +0.31 kg/m², 95% CI −1.33 to 1.95, $p=0.705$; 12 months −0.76 kg/m², 95% CI −2.63 to 1.12, $p=0.420$). No significant sex × group interaction was detected (6 months $p=0.653$; 12 months $p=0.454$).

OGTT 1-Hour glucose threshold analysis

A greater proportion of adolescents in the metformin group exceeded the 1-hour glucose threshold of ≥ 155 mg/dL compared to the non-metformin group ($p<0.050$). Among those with 1-hour glucose ≥ 155 mg/dL, baseline HOMA-IR was significantly higher (median 8.2 (IQR 6.1–10.5) vs. 4.8 (IQR

3.2–6.7), $p < 0.001$). In univariable logistic regression analysis, metformin use was associated with significantly higher odds of having a 1-hour glucose level ≥ 155 mg/dL (unadjusted OR 3.2, 95% CI 1.4–7.3; $p = 0.006$).

Discussion

This real-world longitudinal study examined the association between metformin use and metabolic trajectory in adolescents with obesity. The principal findings showed that adolescents receiving metformin exhibited significantly worse baseline metabolic profiles, including higher BMI, fasting insulin, HOMA-IR, HbA1c, and uric acid, consistent with confounding by indication (22). Both metformin and non-metformin groups demonstrated a characteristic pattern of early improvement at 6 months followed by partial rebound at 12 months across multiple metabolic parameters. After adjustment for baseline covariates, the metformin group was associated with persistently higher fasting insulin and HOMA-IR at 6 months, with differences attenuating by 12 months. Critically, mixed effects models revealed a significant time effect but no significant time $\times$ treatment interaction, indicating that no significant association was observed between metformin use and independent alteration of metabolic trajectory beyond lifestyle modification alone (23,24). Baseline OGTT analysis demonstrated compensatory hyperinsulinemia at all post-load time points in the metformin group, and a 1-hour glucose threshold ≥ 155 mg/dL identified a high-risk metabolic phenotype with threefold higher odds of metformin prescription (25,26).

The observed baseline differences between metformin and non-metformin groups underscore a fundamental challenge in real-world observational studies. Adolescents receiving metformin had significantly higher BMI, fasting insulin, and HOMA-IR, reflecting clinician judgment to initiate pharmacotherapy in patients with more severe metabolic derangement (27). This finding is consistent with ADA guidelines recommending metformin for youth with prediabetes or T2DM, particularly those with marked insulin resistance (28). The significantly elevated HbA1c and uric acid in the metformin group further support the interpretation that these patients represented a higher-risk phenotype at baseline (29).

Importantly, randomized controlled trials have demonstrated modest metformin efficacy when baseline characteristics are balanced through randomization (30,31). The present findings align with previous real-world evidence suggesting that the apparent lack of additional benefit associated with metformin may reflect inadequate control for baseline confounding rather than true pharmacological inefficacy (32,33). However, the observational design of this study precludes definitive conclusions regarding treatment efficacy.

Both groups showed a similar pattern over time: metabolic parameters improved at 6 months, then partially worsened by 12 months. This trend was seen in BMI, insulin resistance markers, lipids, and liver enzymes. The temporal pattern likely reflects reduced adherence to lifestyle changes over time and the metabolic effects of ongoing pubertal development. The key finding was the lack of a significant time $\times$ treatment interaction, indicating that no significant association was

observed between metformin use and independent modification of the metabolic trajectory.

OGTT results showed clear compensatory hyperinsulinemia in the metformin group, with insulin levels significantly higher at all post-load time points and in total insulin exposure (34). This likely reflects a β -cell response to severe insulin resistance. The 1-hour OGTT glucose threshold of ≥ 155 mg/dL emerged as a clinically relevant marker of high-risk metabolic phenotype, with adolescents exceeding this threshold demonstrating threefold higher odds of metformin prescription and significantly higher baseline HOMA-IR (25,35,36).

Several unmeasured confounding factors may have influenced the observed associations and warrant consideration. Pubertal stage is a critical determinant of insulin sensitivity, with physiological insulin resistance peaking during mid-puberty (Tanner stages 3–4) and improving thereafter (37). Differences in pubertal timing between groups could have contributed to differences in metabolic trajectory; however, pubertal staging data were not systematically collected in this retrospective cohort.

Family history of T2DM is a strong predictor of insulin resistance and future diabetes risk in adolescents with obesity (28). While family history was considered in clinical decision-making regarding metformin initiation, it was not systematically documented and could not be included in adjusted analyses. Similarly, socioeconomic status influences access to healthy foods, opportunities for physical activity, and adherence to medical recommendations, but was not captured in this study (38).

Dietary quality and physical activity level are fundamental determinants of metabolic outcomes in pediatric obesity (5,6). Although all participants received standardized lifestyle counseling, individual variability in adherence and engagement was substantial and was assessed only through self-report. Objective measures of dietary intake (e.g., food diaries, 24-hour recalls) and physical activity (e.g., accelerometry) were not systematically collected, limiting our ability to adjust for these critical confounders.

Adherence to lifestyle recommendations likely varied considerably between individuals and over time, contributing to the observed pattern of early improvement followed by partial rebound. The lack of objective adherence measures represents a significant limitation. Similarly, while medication adherence was assessed through self-report in the metformin group, objective measures (e.g., pill counts, pharmacy refill data) were not available.

These unmeasured confounders may have contributed to residual confounding in the adjusted analyses. The observational design of this study precludes definitive conclusions regarding the independent effect of metformin on metabolic outcomes, and prospective randomized trials with comprehensive assessment of confounding factors are needed.

The findings of this study have important implications for clinical practice. The absence of a significant association between metformin use and independent alteration of metabolic trajectory suggests that pharmacotherapy should not be viewed as a substitute for intensive lifestyle modification (27,39). While metformin may provide modest short-term benefits in selected

patients, particularly those with marked hyperinsulinemia or prediabetes, the present results indicate that these benefits are not sustained beyond 6 to 12 months in real-world settings (10,32). The early improvement–late deterioration pattern observed in both groups underscores the critical importance of sustained behavioral support (38).

The 1-hour OGTT glucose threshold of ≥ 155 mg/dL may serve as a useful clinical tool for risk stratification, identifying adolescents with obesity who are at higher risk for progression to T2DM and who may warrant more intensive monitoring and intervention (25,36).

Limitations

Several limitations must be acknowledged. The retrospective, non-randomized design is inherently susceptible to confounding by indication (32). Although statistical adjustment was performed, residual confounding from unmeasured variables (e.g., pubertal stage, family history of diabetes, socioeconomic status, dietary patterns, physical activity level, adherence to lifestyle recommendations) cannot be excluded (28). The absence of objective data on medication adherence, dosing regimens, and concurrent lifestyle intervention intensity represents a critical limitation (10,33). The modest sample size ($n=96$, with only 32 in the metformin group) limited statistical power to detect small-to-moderate effect sizes (9). The single-center design may limit generalizability to other populations and healthcare settings.

Importantly, this observational study cannot establish causality or definitively determine the efficacy of metformin treatment. The observed associations may reflect unmeasured confounding, selection bias, or other factors inherent to real-world clinical practice. Prospective randomized controlled trials with comprehensive assessment of confounding factors, objective adherence measures, and longer follow-up periods are needed to definitively evaluate the efficacy of metformin in adolescents with obesity.

Conclusion

In this real-world observational cohort of adolescents with obesity, those treated with metformin exhibited a significantly more adverse metabolic profile at baseline, characterized by higher adiposity and more pronounced insulin resistance. Although both treated and non-treated groups demonstrated meaningful improvements in anthropometric and metabolic parameters at 6 months, these effects were not sustained at 12 months, indicating limited long-term durability.

After adjustment for baseline covariates, no significant association was observed between metformin use and independent alteration of long-term metabolic trajectory beyond lifestyle modification alone. These findings suggest that metformin prescription in routine clinical practice reflects baseline disease severity; however, the observational design of this study precludes definitive conclusions regarding treatment efficacy.

The early improvement followed by partial rebound observed in both groups underscores the critical importance of sustained lifestyle modification and ongoing behavioral support in the management of pediatric obesity. The 1-hour OGTT glucose

threshold of ≥ 155 mg/dL may serve as a useful tool for identifying adolescents at higher metabolic risk who warrant more intensive monitoring and intervention.

Prospective randomized controlled trials with comprehensive assessment of confounding factors, objective adherence measures, and longer follow-up periods are needed to definitively evaluate the efficacy of metformin in adolescents with obesity and to identify subgroups most likely to benefit from pharmacotherapy.

Ethics committee approval

This study was conducted in accordance with the Helsinki Declaration Principles. The study was approved by Ankara Bilkent City Hospital (November 19, 2025, reference number: 1/1866/2025).

Contribution of the authors

Medical Practices: SKC, GB, EK, SD, HS,FG Concept: SKC, GB, Design:SKC, GB, Data collection: SKC, GB, EK, SD, HS,FG, Analysis: SKC, EK, SD, HS, Literature Search: SKC, EK, SD, HS , Writing: SKC, GB, EK, SD, HS,FG

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Conflict of interest

The authors declare that there is no conflict of interest.

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