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Effects of Low Dose Metformin in Adolescents with Type I Diabetes Mellitus: A Randomized, Double-Blinded Placebo-Controlled Study

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Abstract

Background—Insulin resistance increases during adolescence in those with type 1 diabetes (T1DM), complicating glycemic control and potentially increasing cardiovascular disease (CVD) risk. Metformin, typically used in type 2 diabetes (T2DM), is a possible adjunct therapy in T1DM to help improve glycemic control and insulin sensitivity.

Objective—We hypothesized that metformin would improve metabolic parameters in adolescents with T1DM.

Design, Setting, and Participants—This randomized, double-blinded, placebo-controlled trial included 74 pubertal adolescents (ages 13–20 years) with T1DM. Participants were randomized to receive either metformin or placebo for six months. HbA1c, insulin dose, waist circumference, BMI, and blood pressure were measured at baseline, 3 and 6 months, with fasting lipids measured at baseline and 6 months.

Results—Total daily insulin dose, BMI Z-score and waist circumference significantly decreased at 3 and 6 months compared to baseline within the metformin group, even among normal-weight participants. In placebo group, total insulin dose and systolic blood pressure increased significantly at 3 months and total insulin dose increased significantly at 6 months. No significant

change was observed in HbA1c at any time point between metformin and placebo groups or within either group.

Conclusions—Low-dose metformin likely improves BMI as well as insulin sensitivity in T1DM adolescents, as indicated by a decrease in total daily insulin dose. The decrease in waist circumference indicates that fat distribution is also likely impacted by metformin in T1DM. Further studies with higher metformin doses and more detailed measurements are needed to confirm these results, their underlying mechanisms, and potential impact on CVD in T1DM youth.

Keywords

metformin; Type 1 Diabetes Mellitus; adolescents; insulin resistance

Introduction

There is an increased risk of cardiovascular disease in Type 1 Diabetes Mellitus (T1DM) (1, 2), similar to that seen in T2DM (3). IR is clearly related to cardiovascular disease (CVD) in Type 2 Diabetes Mellitus (T2DM) (4). Therefore, interest in the role of insulin resistance (IR) in T1DM has grown (5). In fact, we demonstrated that adolescents with T1DM have IR as assessed by hyperinsulinemic euglycemic clamp, and early cardiac dysfunction, even with normal body mass index (BMI) (6). We also recently reported that estimated IR predicts increased CVD risk factors in T1DM adolescents (7).

In youth with T1DM, the hormonal, growth and body composition changes characteristic of puberty make diabetes especially difficult to control because they worsen IR (8, 9), especially in girls (10). The high insulin doses required to overcome IR may also be accompanied by excessive weight gain. BMI of T1DM adolescents increases at a faster rate than non-diabetic adolescents (11), which can cause body image problems, particularly in girls, further complicating compliance with a treatment that is restrictive and difficult to accept for teenagers. Finally, obesity is increasing in T1DM youth overall (12,13), and worsens IR. Thus, better diabetes management strategies are needed during adolescence to help delay the onset of CVD, retinopathy and nephropathy (14).

Metformin is an oral anti-hyperglycemic agent commonly used in treating T2DM. Metformin increases insulin sensitivity in T2DM by mechanisms including lowering hepatic glucose output and increasing peripheral uptake of glucose, especially in the muscle (15). In adults with T1DM, adding metformin improved insulin sensitivity while lowering insulin requirements, with conflicting results regarding mean daily blood glucose and BMI (16–20). While metformin is more widely studied in the adult T1DM population, there are a few small studies in adolescents, showing improved HbA1c (8, 21–23). A large trial such as ours had previously not yet been performed in an adolescent population with T1DM. We hypothesized that the increased insulin sensitivity caused by the administration of metformin might improve glycemic control in adolescents with poorly controlled T1DM.

Experimental Design and Methods

Subjects

Participants were recruited from the patient population seen at the Barbara Davis Center for Childhood Diabetes as well as from the Denver metro area. The study was approved by the UCD Institutional Review Board, and appropriate consent and assent was obtained.

Inclusion criteria included age between 13–20 years, with at least a Tanner IV sexual maturation rating, and HbA1c levels higher than 8.5% at the two clinic visits prior to the screening visit. All participants had T1DM, as confirmed by the presence of 1 or more T1DM-associated antibodies (GADA, IA-2, or if done at the time of initial diagnosis, insulin), with a diabetes duration of at least one year.

Participants who met the criteria were selected on a first come first served basis. Creatinine levels were measured prior to enrollment, and adolescents with evidence of renal impairment (serum creatinine level greater than 1.4 mg in females or 1.5 mg in males) were excluded. Other reasons for exclusion included pregnancy, 2 or more episodes of diabetic ketoacidosis (DKA) in the preceding 12 months, preexisting hypertension requiring therapy, retinopathy greater than stage 2, significant non-compliance in the preceding 12 months (multiple missed injections), and having known severe psychiatric disorders.

Study Design

The study was a randomized, double-blinded, placebo-controlled study to test the effects of the addition of 6 months of 500 mg of metformin two times daily to the insulin regimen of adolescents with T1DM. 1000 mg of metformin was chosen due to initial potential concerns of hypoglycemia at the 2000 mg dose typically used in type 2 diabetes. Participants were asked to come to 5 visits during the 6 month study period, at intervals of 6 weeks. Participants were assigned either metformin or a placebo following a table of random numbers, distributed in batches of 100 appropriately-coded tablets at the six-week follow-up visits. The placebo was prepared by Bristol-Myers Squibb and appeared identical to the metformin tablets. Participants were asked to test their blood sugars 3–4 times daily and to refrain from changes in their activity pattern during the study. Insulin doses were initially adjusted after 1–2 weeks by telephone or fax transmission of blood glucose levels measured at home. Thereafter, the doses were adjusted as needed or at the scheduled visits.

At the 0, 3 and 6 month visits, HbA1c, anthropometry and blood pressure were obtained. Blood pressure was measured after 5 minutes of rest in a seated position. Three blood pressure measurements were taken and averaged. Waist circumference was measured using a fiberglass tape measure, with the participant standing erect with abdomen relaxed, arms at sides, and feet together. The waist circumference was taken at end of expiration at the midpoint between the highest point of the iliac crest and the lowest part of the costal margin in the mid-axillary line. Two measurements were taken, or a third if the first two measurements disagreed by > 0.5 cm.

Fasting total and HDL- cholesterol levels were obtained at the 0 and 6 month visits, and study medication compliance was recorded at each visit by pill counts. The incidences of

severe hypoglycemic events requiring medical intervention and of ketonuria were noted, and the history of intercurrent illness and additional medications were obtained following routine clinic procedures. Ketone testing was recommended whenever blood sugars exceeded 350mg/dL. Urine pregnancy tests were performed on all female participants at the clinic visits.

Outcomes

The primary outcome analyzed was the level of HbA1c after 6 months. Secondary outcomes were HbA1c level after 3 months, total daily insulin dose (in units and units/kg), blood pressure, BMI, and waist circumference at 3 and 6 months as well as fasting lipids at 6 months.

Statistical Analysis

Data are reported as mean $\pm$ standard deviation. An α level of <0.05 was considered statistically significant. Sample size calculations showed that sixty participants (thirty in each group) were required to detect a 15% decrease in HbA1c, with a power of 0.95 and an α of 0.05. A 25% drop-out rate was assumed, therefore eighty subjects were recruited. Variables were checked for the statistical assumption of normality using plots and the Shapiro-Wilk test. HbA1c, high density lipoprotein cholesterol (HDL), and total cholesterol were skewed and a natural log transformation was applied. Analyses were then performed on the transformed data and with the untransformed variables. Since transformation did not change the results, the un-transformed values are presented as mean $\pm$ SD. Baseline characteristics were compared between the two groups using an independent sample t-test for continuous variables and Chi Square Test of Independence or Fisher's Exact test for categorical variables. Mixed models longitudinal data analysis was used to assess HbA1c and other variables of interest over time using an AR(1) variance structured for equally spaced time points. A cell means model produced and compared estimates at baseline, 3 months, and 6 months. Data were analyzed as intent to treat.

Results

80 participants were randomized; 40 to metformin and 40 to placebo. In the metformin group, 6 participants dropped out before the 3 month visit, and an additional 6 dropped out before the final 6 month visit. In the placebo group, 6 participants dropped out before the 3 month visit and 3 dropped out before the final 6 month visit. Subjects that dropped out were due to loss to follow-up (moving or inability to participate due to schedule changes). No participants dropped out due to inability to tolerate the medication, hypoglycemia or diabetic ketoacidosis. Baseline characteristics in those subjects who dropped out did not differ significantly from the subjects retained (data not shown).

Mean age for all participants was 16 years old and approximately half of participants were boys (59%). Approximately 31% of baseline participants were overweight or obese (30% in the metformin group and 39% in the placebo group). Ethnicity was 88% Caucasian, 7% Hispanic, 3% African American and 2% other. Baseline characteristics of the participants subdivided by gender are presented in Table 1. Of note, females had significantly higher

total cholesterol (mainly due to one female with a very elevated cholesterol level) and as expected, males had significantly lower HDL and higher weight and height but similar BMI, and higher total daily insulin dose (in units/day but not in units/kg/day) than females.

The baseline characteristics of the metformin and placebo group are presented in Table 2. At baseline, the placebo and metformin groups were similar in HbA1c, diabetes duration, age, weight, height, BMI, BMI z-score, systolic blood pressure, total cholesterol, HDL, total daily insulin dose (in units and units/kg), and waist circumference, except for diastolic blood pressure which was slightly lower in the placebo group (Table 2).

Comparisons of results between the metformin and placebo groups and within the metformin and placebo groups are presented in Tables 3 and 4, respectively. HbA1c levels did not significantly change from 0 to 3 or 6 months in the metformin group or the placebo group and there was no significant difference in HbA1c between the metformin and placebo groups at any time point. However, when female participants were analyzed separately, girls in the metformin group tended to have a lower HbA1c at 3 months (9.79 ± 1.67 to 9.39 ± 1.93 %, $p=0.06$), but boys did not (9.36 ± 0.88 to 9.32 ± 1.29 %, $p=0.9$). Similarly, when the overweight/obese participants in the metformin group were analyzed separately, they had a significantly lower HbA1c at 3 months (9.42 ± 1.06 to 8.78 ± 1.17 %, $p=0.03$), and tended to have a lower HbA1c at 6 months (9.42 ± 1.06 to 8.84 ± 1.09 %, $p=0.08$), whereas normal weight participants had no significant HbA1c changes from baseline.

In the metformin group there was a significant decrease in daily insulin dose in units and units/kg between 0 and 3 months (units, $p<0.03$; units/kg, $p=0.035$) as well as between 0 and 6 months (units, $p<0.05$; units/kg $p=0.014$). In contrast, in the placebo arm the total daily insulin dose in units increased significantly from baseline to 3 ($p=0.03$) and 6 months ($p=0.002$), and was unchanged in units/kg at 3 ($p=0.93$) and 6 months ($p=0.998$). When analyzed by gender, males in the metformin group had a significant decrease in daily insulin dose in units/kg at 6 months (1.25 ± 0.24 to 1.10 ± 0.18 units/kg, $p<0.04$), as did females (1.18 ± 0.24 to 1.14 ± 0.24 , $p<0.05$). Overweight/Obese participants had no trend towards a change in insulin dose, whereas normal weight participants reflected the significant overall group changes (1.23 ± 0.24 units/kg at baseline to 1.18 ± 0.28 at 3 months, $p=0.1$; 1.09 ± 0.21 at 6 months, $p=0.004$).

There was also a significant decrease in BMI z-score within the metformin group between baseline and 3 months ($p=0.02$) and between baseline and 6 months ($p=0.01$). Similarly, there was a significant decrease in waist circumference within the metformin group between baseline and 3 months ($p=0.003$) and between baseline and 6 months ($p<0.02$). When our data was sub-analyzed by gender, females had a significant reduction in waist circumference at 3 months (74.8 ± 9.1 to 72.6 ± 8.7 cm, $p<0.02$), and a trend towards a reduction at 6 months (74.8 ± 9.1 to 73.9 ± 8.8 cm, $p=0.11$). Females also tended to decrease their BMI z-score at 3 months (0.77 ± 0.6 to 0.65 ± 0.64 , $p=0.10$) and had a significant reduction in BMI z-score at 6 months (0.77 ± 0.6 to 0.70 ± 0.59 , $p=0.02$). Males, in contrast had no significant change in waist circumference or BMI z-score. Among overweight/obese participants, waist circumferences tended to decrease from at 3 months (84.9 ± 6.5 to 82.9 ± 5.0 cm, $p=0.12$) and at 6 months (84.9 ± 6.5 to 83.2 ± 5.3 cm, $p=0.06$), as did BMI Z-score at 6 months (1.45

± 0.14 to 1.25 ± 0.33 , $p=0.07$). Similarly, waist circumference among normal weight participants decreased significantly at 3 months (73.6 ± 7.5 to 71.8 ± 7.4 cm, $p=0.01$), and tended to do so at 6 months (73.6 ± 7.5 to 72.7 ± 6.8 , $p=0.12$), as did BMI z-score (0.49 ± 0.53 at 0 months to 0.33 ± 0.61 at 3 months, $p<0.05$; 0.41 ± 0.47 at 6 months, $p=0.10$).

Finally, a significant increase in systolic blood pressure was noted in the placebo group at 3 months compared to baseline ($p=0.03$). There were no significant changes between the metformin and placebo groups in the other parameters.

Compliance, defined as taking at least 75% of all pills, was 1.4 ± 0.5 pills in the metformin group and 1.6 ± 0.3 pills in the placebo group ($p=0.06$) at 3 months. At 6 months, compliance for the metformin group was 1.7 ± 0.7 pills and for the placebo group was 1.3 ± 0.6 pills ($p<0.03$). The metformin was well tolerated with no reported severe hypoglycemia, diabetic ketoacidosis or other related severe adverse events. There was no difference between groups in gastrointestinal symptoms (metformin: nausea 8%, diarrhea 7%, abdominal pain 1% vs. placebo: nausea 8%, diarrhea 6%) or ketones, and no subjects had symptoms severe enough to require study medication dose reductions.

Discussion

We report significant decreases in insulin dose, BMI z-score and waist circumference with low-dose metformin at 3 months and 6 months compared to baseline in T1DM youth in comparison to increased insulin dose at the same time points in the placebo group. No significant change was observed in HbA1c levels. There have been only a few studies examining the use of metformin specifically in the adolescent T1DM population, of which two were open-label with very small subject numbers. In contrast, our study involved a much larger subject population than previously reported (74 subjects as opposed to the next largest study in the adolescent population which had 30 subjects), longer follow-up and also addresses differences in response to metformin by sex and BMI status.

Regarding glycemia, we found no significant change in HbA1c levels with metformin which differs from results from other adolescent studies (8, 22–24). However, two of these studies were open label and had only 9 or 10 participants, one of which included subjects up to age 45 years (24). Possible explanations for the discrepancy between our HbA1c results with these studies are that our study's total daily metformin dose of 500mg twice a day was among the lowest doses given, or that adolescents with poor control were targeted. However, HbA1c findings in adult studies vary, with some reporting reductions in HbA1c (17, 18), two reporting a transient reduction of HbA1c levels at 3 months that disappeared at 6 months (19, 20) and others confirming our results of a reduction in insulin dose without any effect on HbA1c (16). Moreover, our overweight/obese and female participants did have reductions in HbA1c, whereas boys and normal-weight participants did not. Our finding of a significant decrease in insulin dose with metformin in T1DM adolescents, regardless of gender, suggests sustained improved insulin sensitivity (16). This finding is supported by shorter term results from Hamilton *et al* ($n=29$) at 3 months and (23) Urakami *et al* ($n=9$) at 3 and 12 months of use (22). In contrast, Gomez *et al* reported no change in insulin dosages ($n=10$), but their sample size may have been underpowered to see such differences (24).

Similarly, Sarnblad *et al* (n=24) found no change in insulin dose at 3 months, but insulin sensitivity as measured by hyperinsulinemic euglycemic clamp improved significantly in the metformin group. Thus, insulin dose may lack sensitivity in detecting changes in IR in adolescents. In adult T1DM studies, many groups reported a significant decrease in total daily insulin dose (16–20,26, 27). This finding is supported by data from Gin *et al*, who reported that metformin improved insulin sensitivity as measured by a hyperinsulinemic euglycemic clamp in 10 adult T1DM subjects (28). Our results are also confirmed by a meta-analysis published in 2010, which reported a reduction in insulin dose but no change in HbA1c when combining all available adolescent and adult T1DM metformin data (25). In contrast to the HbA1c findings, our overweight/obese participants did not have detectable reductions in insulin dose, whereas normal-weight participants did, but this may be due to the smaller sample size of overweight/obese youth.

Regarding weight and body composition, we report a significant improvement in BMI z-score and waist circumference in both overweight/obese and normal weight adolescents with low-dose metformin, suggesting a decrease in central adiposity. The only adolescent study to report waist circumference, Sarnblad *et al*, did not observe any significant changes in BMI or waist circumference between groups (8), but their sample size (n=24) was much smaller than ours and follow-up period was shorter at only 3 months. Only one adult study assessed waist circumference and found no significant change between baseline and 1 year, although they did report a significant decrease in hip circumference after 1 year (20). In support of our BMI findings,, Urakami *et al* (n=9) found a significant decrease in BMI after 12 months of metformin (22). BMI was not measured in any of the adult studies, although body weight was frequently measured, with several studies reporting no significant change (16, 17,19, 27) and several seeing a significant decrease with metformin (18, 20, 26). Interestingly, when our data was sub-analyzed by gender, only females had a significant reduction in waist circumference or in BMI z-score.

While we found no changes in lipids at 6 months, Urakami *et al* also found a significant decrease in total cholesterol at 12 months of metformin use (22). Similarly, Lund *et al* and Meyer *et al* both found significant decreases in total and LDL cholesterol levels in all patients (27, 29). The other studies either did not find a significant change or lipid levels were not assessed. Our lower dose of metformin or the shorter duration of treatment may explain these differences.

Our study was a large, placebo-controlled double-blinded study, but does have several limitations. First, although insulin dose changes imply an increase in insulin sensitivity, there was no formal measure of IR such as a hyperinsulinemic euglycemic clamp, physical activity changes over time, hormonal profiles in females, or glycemic variability. In addition, fat distribution was only estimated by waist circumference data, and lipids were not measured at the 3-month visit. A higher dose of metformin may also have led to more significant effects. Finally, compliance is a potential limitation, although the metformin group was actually more compliant with study medication by the end of the study. In conclusion, although there have been a few studies performed previously to assess whether metformin could be used to help improve glycemic control in T1DM, very few have been

with adolescents. These few studies were small, or were not placebo controlled, double blinded studies such as ours, making our study important to the literature.

Our results show positive impacts of metformin in T1DM youth on insulin sensitivity, BMI and body composition, which might translate to decreased risk of CVD and other complications in the future. Our significant result in the normal-weight group also argues that metformin may be appropriate for both normal-weight youth with T1DM, as well as the typically considered overweight/obese population. The higher compliance in the metformin group argues that it was well tolerated, and a higher dosage was previously shown to have a positive benefit on HbA1c levels. Therefore, further investigation of higher doses in a larger subject pool is warranted. Thus, future studies with hyperinsulinemic euglycemic clamps to investigate tissue-specific changes in insulin sensitivity, sex steroids, physical activity monitoring, and continuous glucose monitoring are now underway in this population with a higher metformin dose to address some of the limitations observed in this study. In addition, future studies will also include additional markers of CVD and CV function, to assess the impact of metformin on reducing T1DM-associated complications.

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Abbreviations

T1D	Type 1 Diabetes
CVD	cardiovascular disease
T2D	Type 2 Diabetes
IR	insulin resistance
BMI	body mass index

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Table 1

Baseline Characteristics by Gender

	Means $\pm$ SD and p-values for comparisons by group		
Variable	Male	Female	p-value
HbA1C (%)	9.4 $\pm$ 0.9	9.8 $\pm$ 1.7	0.24
Age (years)	16.1 $\pm$ 1.7	16.0 $\pm$ 1.5	0.79
BMI (kg/m ²)	23.1 $\pm$ 3.1	23.6 $\pm$ 3.0	0.50
BMI Z-score	0.75 $\pm$ 0.66	0.77 $\pm$ 0.60	0.89
Total Cholesterol (mg/dL)	160.0 $\pm$ 30.0	193.8 $\pm$ 43.3	<0.001
HDL (mg/dL)	49.3 $\pm$ 12.9	56.6 $\pm$ 9.6	0.009
SBP (mm Hg)	123.3 $\pm$ 15.5	120.1 $\pm$ 9.2	0.29
DBP (mm Hg)	71.9 $\pm$ 8.2	70.8 $\pm$ 7.5	0.56
Duration of Diabetes (years)	7.0 $\pm$ 3.6	6.4 $\pm$ 3.7	0.50
Height (cm)	172.9 $\pm$ 9.9	162.0 $\pm$ 7.1	<0.001
Total Daily Insulin Dose (U/day)	87.4 $\pm$ 25.8	71.8 $\pm$ 13.9	0.002
Total Daily Insulin Dose (U/kg/day)	1.25 $\pm$ 0.2	1.17 $\pm$ 0.2	0.10
Waist Circumference (cm)	78.5 $\pm$ 8.9	74.8 $\pm$ 9.1	0.09
Weight (kg)	69.4 $\pm$ 12.9	62.4 $\pm$ 11.0	0.017

Note. Results presented as Mean $\pm$ SD.

*
p < 0.05

Table 2

Baseline Characteristics of Metformin versus Placebo Groups

	Means $\pm$ SD and p-values for comparisons by group		
Variable	Metformin	Placebo	p-Value
HbA1c (%) (mmol/mol)	9.5 $\pm$ 1.3 80.7 $\pm$ 14.4	9.4 $\pm$ 1.1 79.7 $\pm$ 11.5	0.77
Age (years)	15.9 $\pm$ 1.7	16.0 $\pm$ 1.6	0.83
Body Mass Index (kg/m ²)	23.5 $\pm$ 3.0	24.3 $\pm$ 4.1	0.33
BMI Z-score	0.77 $\pm$ 0.63	0.81 $\pm$ 0.80	0.84
Total Cholesterol (mg/dL)	179.1 $\pm$ 41.8	176.8 $\pm$ 33.6	0.81
HDL (mg/dL)	53.3 $\pm$ 11.6	49.2 $\pm$ 13.9	0.21
SBP (mm Hg)	121.6 $\pm$ 12.6	117.3 $\pm$ 12.2	0.16
DBP (mm Hg)	71.2 $\pm$ 7.8	67.3 $\pm$ 7.4	0.04*
Diabetes Duration (years)	6.7 $\pm$ 3.6	6.3 $\pm$ 3.5	0.60
Height (cm)	167.1 $\pm$ 10.2	166.0 $\pm$ 9.3	0.63
Total Daily Insulin Dose (U/day, range)	79.6 $\pm$ 21.4 (49–130)	76.0 $\pm$ 23.8 (41–173)	0.51
Total Daily Insulin Dose (U/kg/day, range)	1.21 $\pm$ 0.24 (0.9–1.6)	1.15 $\pm$ 0.32 (0.6–2.1)	0.37
Waist Circumference (cm)	77.1 $\pm$ 9.2	76.0 $\pm$ 8.9	0.63
Weight (kg)	65.7 $\pm$ 12.3	67.1 $\pm$ 13.2	0.69

Note. Results presented as Mean $\pm$ SD.*
p < 0.05

Table 3

Difference between Metformin and Placebo Groups at 3 months and 6 months

Variable	Visit	Metformin	Placebo	p-value
HbA1c (%) (mmol/mol)	3	9.4 ± 1.7 78.8 ± 18.0	9.5 ± 1.2 80.3 ± 13.1	0.69
	6	9.2 ± 1.2 77.1 ± 13.3	9.6 ± 1.2 80.9 ± 13.3	0.27
BMI (kg/m ²)	3	23.2 ± 3.0	24.3 ± 3.9	0.18
	6	23.5 ± 2.4	24.7 ± 3.7	0.13
BMI Z-score	3	0.64 ± 0.71	0.78 ± 0.77	0.43
	6	0.70 ± 0.55	0.88 ± 0.69	0.16
Total Cholesterol (mg/dL)	6	177.5 ± 36.4	177.0 ± 35.9	0.97
HDL (mg/dL)	6	52.2 ± 9.5	50.2 ± 14.9	0.57
SBP (mm Hg)	3	119.3 ± 14.0	122.3 ± 12.7	0.36
	6	119.8 ± 14.7	120.6 ± 11.5	0.83
DBP (mm Hg)	3	69.1 ± 10.1	67.9 ± 10.7	0.63
	6	69.4 ± 6.7	69.8 ± 9.5	0.83
Total Daily Insulin Dose (U/day)	3	75.9 ± 20.8	78.1 ± 24.9	0.69
	6	74.2 ± 18.5	79.1 ± 26.2	0.42
Total Daily Insulin Dose (U/kg/day)	3	1.17 ± 0.27	1.16 ± 0.32	0.48
	6	1.12 ± 0.21	1.16 ± 0.34	0.41
Waist Circumference (cm)	3	75.1 ± 8.4	76.2 ± 9.0	0.62
	6	75.7 ± 7.9	77.4 ± 7.7	0.41
Weight (kg)	3	65.6 ± 12.1	67.5 ± 12.5	0.54
	6	66.2 ± 11.2	68.5 ± 11.7	0.46

Note. Results presented as Mean ± SD.

Table 4
Longitudinal Within-Group Changes for Metformin and Placebo Groups Relative to Baseline

Metformin Within Group comparison				Placebo Within Group comparison			
Variable	Visit	Metformin	p-value	Variable	Visit	Placebo	p-value
HbA1c (%) (mmol/mol)	3	9.4 ± 1.7 78.8 ± 18.0	0.39	HbA1c (%) (mmol/mol)	3	9.5 ± 1.2 80.3 ± 13.1	0.78
	6	9.2 ± 1.2 77.1 ± 13.3	0.70		6	9.6 ± 1.2 80.9 ± 13.3	0.34
BMI (kg/m ²)	3	23.2 ± 3.0	0.14	BMI (kg/m ²)	3	24.3 ± 3.9	0.83
	6	23.5 ± 2.4	0.17		6	24.7 ± 3.7	0.27
BMI Z-score	3	0.64 ± 0.71	0.02	BMI Z-score	3	0.78 ± 0.77	0.34
	6	0.70 ± 0.55	0.01		6	0.88 ± 0.69	0.74
Total Cholesterol (mg/dL)	6	177.5 ± 36.4	0.43	Total Cholesterol (mg/dL)	6	177.0 ± 35.9	0.53
HDL (mg/dL)	6	52.2 ± 9.5	0.57	HDL (mg/dL)	6	50.2 ± 14.9	0.90
SBP (mm Hg)	3	119.3 ± 14.0	0.26	SBP (mm Hg)	3	122.3 ± 24.9	0.03*
	6	119.8 ± 14.7	0.35		6	120.6 ± 11.5	0.35
DBP (mm Hg)	3	69.1 ± 10.1	0.20	DBP (mm Hg)	3	67.9 ± 10.7	0.80
	6	69.4 ± 6.7	0.23		6	69.8 ± 9.5	0.16
Total Daily Insulin Dose (U/day)	3	75.9 ± 20.8	0.028*	Total Daily Insulin Dose (U/day)	3	78.12 ± 24.87	0.030*
	6	74.2 ± 18.5	0.048*		6	79.1 ± 26.2	0.002*
Total Daily Insulin Dose (U/kg/day)	3	1.17 ± 0.27	0.035*	Total Daily Insulin Dose (U/kg/day)	3	1.16 ± 0.32	0.93
	6	1.12 ± 0.21	0.014*		6	1.16 ± 0.34	0.99
Waist Circumference (cm)	3	75.1 ± 8.4	0.003*	Waist Circumference (cm)	3	76.2 ± 9.0	0.30
	6	75.7 ± 7.9	0.015*		6	77.4 ± 7.7	0.41
Weight (kg)	3	65.6 ± 12.1	0.57	Weight (kg)	3	67.5 ± 12.5	0.40
	6	66.2 ± 11.2	0.97		6	68.5 ± 11.7	0.22

Note. Results presented as Mean ± SD.

* p<0.05 in comparison to baseline within group.