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Randomized, Controlled Trial of Metformin for Children with Type 2 Diabetes Mellitus

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Abstract: **Background: Metformin therapy for adults and children with type 2 diabetes mellitus is well established. However, its role in the treatment of insulin resistance and obesity in children and adolescents has not been clearly defined. Objectives: We evaluated the effects of metformin on body composition and insulin sensitivity in children with exogenous obesity. Design and context: Patients referred to a pediatric endocrinology clinic were included in a randomized, double-blind, crossover trial. , patients: 28 patients (13 men) aged 9 to 18 participated in the study. Intervention: Patients received metformin (1 g twice daily) and placebo for 6 months, each with an elimination period of 2 weeks. Results: Mean age of subjects at baseline was 12.5 ± 2.2 years, mean body mass index z-score was 2.54 (range, 1.93–2.85). Metformin was more effective than placebo for weight (–4.35 kg, P = 0.02), body mass index (–1.26 kg/m2, P=0.002), waist circumference (—2.8 cm, P=0.003), abdominal adipose tissue sc (—52.5 cm2, P=0.0.002) and fasting insulin (—2.2 mU/liter, P = 0.011). IS improved in 45% of metformin and 27% of placebo subjects (P = 0.21). Conclusions: Treatment with metformin in insulin-resistant obese pediatric patients significantly improves body composition and fasting insulin. Although improvement in Si has been noted in many individuals, Si is a less useful parameter for group data analysis, possibly due to the effect of variable conformance and Si change in adolescent.**

Keywords: **Metformin therapy, type 2 diabetes, insulin sensitivity.**

1. INTRODUCTION

Obesity with insulin resistance in the pediatric population represents an increasing treatment challenge. Metformin is a well-known oral hypoglycemic agent used to treat adults with type 2 diabetes and other insulin resistance-related disorders. The positive effect of metformin in young patients with type 2 diabetes was demonstrated in a randomized controlled study (1). Metformin is also useful in children and adolescents with type 1 diabetes and insulin resistance (2-4); girls with polycystic ovarian syndrome or at high risk of developing polycystic ovarian syndrome (5-8); and young patients with nonalcoholic fatty liver disease (9). There is limited data on the role of metformin in obesity-related insulin resistance prior to the development of type 2 diabetes in children. The potential clinical use of metformin in children and adolescents was first described in 1 in a small study from the 1970s that showed a beneficial effect on body weight and insulin levels in obese older children aged 8 to 14 years (10). Subsequent data from pediatric randomized controlled trials have demonstrated improvements in body mass index (BMI), fasting glucose and insulin, and improved lipid profile in exogenously obese insulin-resistant patients treated with metformin (11, 12) and psychotropic drug-induced weight gain (13). However, insulin sensitivity, as measured by the minimal model, did not improve significantly in metformin-treated adolescents compared to

placebo in a controlled, randomized, controlled trial (12), raising the question of whether metformin specifically improves peripheral insulin sensitivity. Insulin. By conducting a randomized, controlled, crossover study, we aimed to clarify the role of metformin treatment in obese children and adolescents, with particular attention to the effects on anthropometry, body fat compartments, and insulin sensitivity parameters.

2. SUBJECTS AND METHODS

Participants were 9 to 18 yr olds referred to the endocrine clinic at The Children's Hospital at Westmead between March 2002 and March 2003 with obesity, as defined by the International Obesity Task Force (14), and clinical suspicion of insulin resistance, as defined by either a fasting insulin (milliunits per liter) to glucose (millimoles per liter) ratio greater than 4. 5 (15) or the presence of acanthosis nigricans.

Exclusion criteria were known type 1 or type 2 diabetes mellitus, contraindications to metformin therapy, and/or magnetic resonance imaging (MRI) scanning and weight greater than 120 kg due to technical difficulties with dual-energy x-ray absorptiometry (DXA) scans.

All parents and patients were given verbal and written information about the study before pro- viding written consent.

This study was approved by The Children's Hospital at Westmead Ethics Committee and registered with the International Standard Randomized Controlled Trial scheme (ISRCTN43267711). Participants were randomized to receive metformin and placebo for 6 months each in a crossover design, with a 2-wk washout period in between.

Block randomization (blocks of four) with stratification by pubertal stage (Tanner 1–2 or Tanner 3–5) was performed by computer- generated random number allocation, and placebo or metformin was dispensed by the hospital pharmacy. All participants and investigators were blinded to the intervention. Both metformin and placebo doses were gradually built up over a 3-wk period to a final dose of 1 g twice daily.

At baseline and 6 and 12 months, participants attended The Children's Hospital at West- mead for clinical assessment including anthropometry, frequently sampled iv glucose tolerance test, DXA imaging, and MRI of the abdomen as detailed below.

At 3 and 9 months, participants underwent clinical assessment and fasting biochemical profile. Liver function tests, serum creatinine, and serum lactate levels were measured every 3 months to assess metformin safety profile.

Pill counts were conducted every 3 months by the hospital pharmacy to calculate percent adherence to therapy based on number of capsules consumed vs. Clinical assessment and anthropometry Waist circumference was calculated from the average of three measures at the level of the umbilicus. calculated from the U. Centers for Disease Control and Prevention reference data 2000 (16).Waist circumference z-scores were calculated from recent multiracial American reference data (17). Pubertal stage was assessed using the standards of Tanner and Whitehouse (18).

Blood pressure was measured on the right arm with an appropriately sized cuff using a DynaMap machine with the subject seated. Acanthosis nigricans was assessed for severity at the neck by a validated scale ranging from grade 0 (not present) to grade 4 (severe: extending anteriorly, visible when the participant is viewed from the front) (19).

This was performed clinically by the principal investigator (S.) and based on clinical photographs by an independent observer. Frequently sampled iv glucose tolerance test After an overnight fast, subjects underwent a 180-min iv glucose tolerance test for minimal model analysis of parameters of insulin sen- sitivity (20).

An iv cannula was inserted into each arm, one for sampling and the other for glucose and insulin boluses. At 20 min 0. 03 U/kg Actrapid insulin (1:10 dilution) was given over 90 sec. Paired insulin and glucose samples were taken at 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 19, 22, 23, 24, 25, 27, 30, 40, 50, 60, 70, 80, 90, 100, 120, 140, 160, and 180 min. The insulin assay was performed on the Immulite analyzer (Diagnostics Products Corp. , Los Angeles, CA) using an immunometric assay. DXA scans were performed on the GE Lunar Prodigy machine (GE Lunar Corp. , Madison, WI) in the Department of Medical Imaging at The Children's Hospital at Westmead. Data obtained from the DXA scans were processed using GE Lunar enCore software (version 6.029; GE Lunar Corp.) to calculate percent total body fat. All subjects were scanned on a 1. 5 Tesla Philips (Best, The Nether- lands) ACS-NT whole-body MRI unit. Analyze software (version 4. 0; Mayo Clinic, Rochester, MN) was used to quantify the surface area (square centimeters) of visceral abdominal adipose tissue (VAAT) and sc abdominal adipose tissue in each of the five slices. The mean of the five slices was used in the final analysis.

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All analyses were performed by the same investigator (S. All analyses were performed by the same investigator (S. For all outcomes, data were analyzed as a simple two-period cross- over trial using Statistical Package for the Social Sciences (SPSS; version 11. 1; Chicago, IL). To assess the effect of metformin vs. placebo, the paired sample t test was used to compare means for normally distributed data and the Wilcoxon signed-ranks test to compare paired medians for nonparametric data. The difference between the means of the two groups was taken as twice the size of the treatment effect (21).

Linear mixed model analysis was per- formed to assess possible confounding effect of change in pubertal stage and poor adherence to therapy on insulin sensitivity.calculated from the U.S. Centers for Disease Control and Prevention reference data 2000 (16).

Waist circumference z-scores were calculated from recent multiracial American reference data (17). Pubertal stage was assessed using the standards of Tanner and Whitehouse (18). Blood pressure was measured on the right arm with an appropriately sized cuffusing a DynaMap machine with the subject seated. The lowest of three measures was recorded.

Routine physical examination was performed before each set of investigations to rule out significant intercurrent illness. Acanthosis nigricans was assessed for severity at the neck by a validated scale ranging from grade 0 (not present) to grade 4 (severe: extending anteriorly, visible when the participant is viewed from the front) (19).

This was performed clinically by the principal investigator (S.S.) and based on clinical photographs by an independent observer.

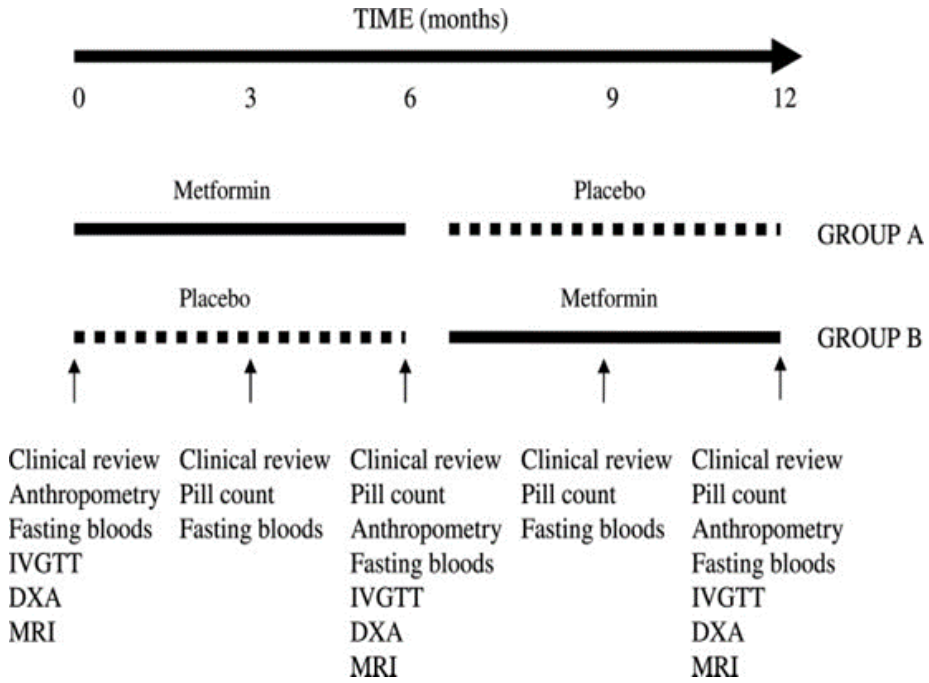

FIG. 1. Time line for investigations. IVGTT, Intravenous glucose tolerance test.

3. RESULTS

Thirty-four patients were referred to the study; five re- fused to participate and one did not meet the inclusion criteria. Twenty-eight patients (13 males) participated in the study.

One participant in group A and three participants in group B discontinued the study due to nonadherence to therapy or social circumstances. Two participants in group A had difficult iv access and did not have a full set of insulin sensitivity data.

The flow of patients through the study is summarized in Fig. There was no difference in baseline characteristics between groups A and B. Metformin treatment effect on anthropometry and body composition Metformin therapy had a significant beneficial treatment effect over placebo for weight, BMI (Fig. 3A), and waist circumference, both as raw measures and z-scores .

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Whereas metformin therapy resulted in a tendency to re- duction in total body fat percentage from DXA measurements (treatment effect 0. 67%), this was not significant (P = 0. 062). Median acanthosis nigricans neck severity score on metformin was 3. 0 (0 – 4) and placebo was 4. 0 (0 – 4), P = 0.304.

Metformin treatment effect on parameters of insulin sensitivity Metformin therapy had a beneficial treatment effect over placebo for fasting insulin (Fig. 3B) and a small but significant beneficial effect for fasting glucose (Table 2). Insulin sensitivity measured from the minimal model improved in 10 of 22 (45%) patients on metformin and six of 22 (27%) patients on placebo (P = 0. 21). There was no significant beneficial treatment effect of metformin over placebo for insulin sensitivity parameters (insulin sensitivity, Sg, AIR, DI, Kg) measured by minimal model analysis (Table 2 and Fig. 3C).

Side effects, adherence to therapy, and safety profile Both metformin and placebo were well tolerated with only two participants (aged 9 yr) unable to tolerate 1 g metformin twice daily due to nausea. Adherence to therapy based on pill counts for the whole group was similar for metformin and placebo (metformin median adherence 78%, range 15–99%; placebo median adherence 78%, range 35–98%; P = 0. 689).

There was no difference in liver function tests, serum creatinine, or lactate levels while on metformin or placebo (se- rum alanine aminotransferase 49. 9 ± 25. 1 vs. U/liter, P = 0.100; serum creatinine 60. 6 ± 9. 7 vs. 4 ± 9. 0 μmol/liter, P = 0. 141; serum lactate 0. 29 ± 0. 47 vs. Role of adherence to therapy and change in pubertal status in insulin sensitivity measures In addition, six patients underwent a change in pubertal stage from Tanner 1–2 to Tanner 3–5 over the 1-yr period. best estimate of fit) was used to assess the possible con- founding effect on insulin sensitivity of poor adherence to therapy and change in pubertal status.

After adjusting for change in pubertal stage and adherence to therapy, insulin sensitivity on metformin was 0. 172 (milliunits per liter)—1 per minute—1 higher [95% confidence interval —0. 146 to 0. 491 (milliunits per

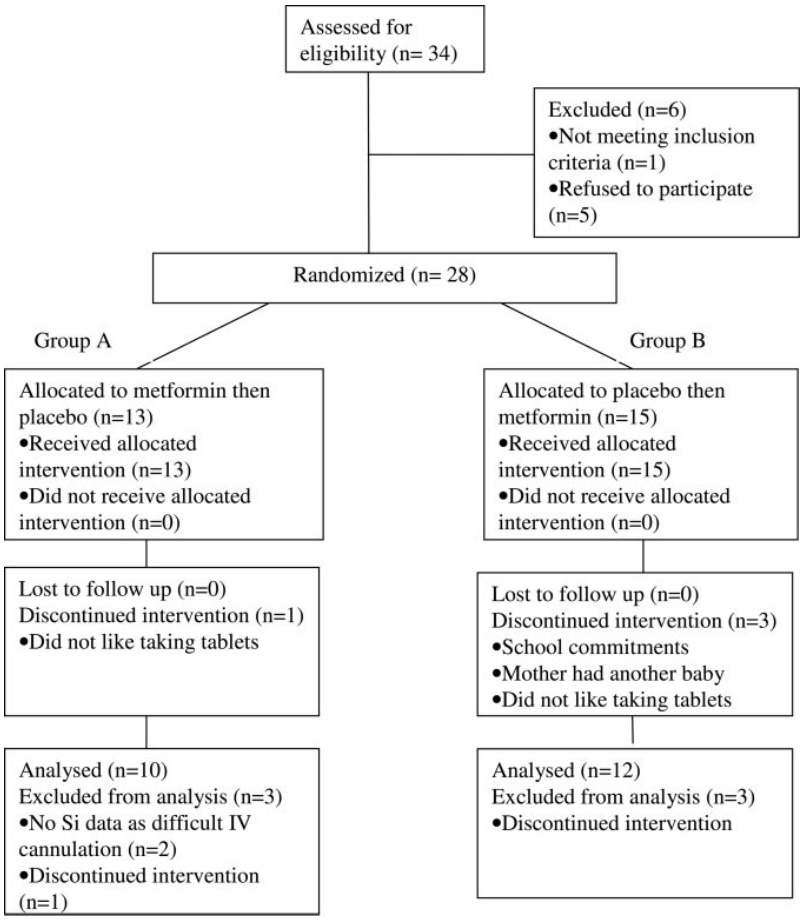

FIG. 2. CONSORT (Consolidated Standard for Reporting Clinical Trials) flow diagram.

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TABLE 1. Baseline characteristics

Feature	Total group (n = 28)	Males (n = 13)	Females (n = 15)	*P* value (males *vs.* females)
Age (yr)	12.5 ± 2.2	12.2 ± 2.7	12.8 ± 1.7	0.50
Weight (kg)	89.9 ± 17.6	84.3 ± 15.2	94.8 ± 18.5	0.19
Weight z-score	2.71 ± 0.52	2.68 ± 0.55	2.73 ± 0.51	0.78
Height (cm)	159.4 ± 10.2	157.8 ± 12.4	160.7 ± 8.1	0.46
Height z-score	0.98 ± 1.14	0.97 ± 1.11	0.98 ± 1.20	0.98
BMI (kg/m^2)	35.2 ± 5.1	33.9 ± 5.4	36.4 ± 4.6	0.20
BMI z-score	2.43 ± 0.28	2.41 ± 0.32	2.46 ± 0.24	0.61
Waist circumference (cm)	106.8 ± 12.3	106.2 ± 12.5	107.4 ± 12.5	0.81
Waist circumference z-score	1.67 ± 0.32	1.58 ± 0.42	1.75 ± 0.20	0.17
Pubertal stage (no. Tanner 1–2:no. Tanner 3–5)	14:14	10:3	4:11	0.02
Systolic blood pressure (mm Hg)	121.2 ± 14.2	123.4 ± 12.5	119.3 ± 15.8	0.46
Diastolic blood pressure (mm Hg)	63.4 ± 8.3	63.5 ± 8.7	63.3 ± 8.2	0.93
Acanthosis nigricans neck score	3.5 (0 – 4)	4 (1– 4)	3 (0 – 4)	0.09

4. DISCUSSION

This study demonstrates that metformin therapy for insulin resistance and obesity in the pediatric population is safe and well tolerated and has a beneficial effect on weight, BMI, waist circumference, sc abdominal fat, fasting insulin, and fasting glucose.

Although a number of patients had improved insulin sensitivity on metformin, this did not reach statistical significance. Our study population was 9 to 18 yr olds referred to the endocrine service for management of obesity and insulin resistance. Many were experiencing relentless weight gain with the development of clinical features of insulin resistance, such as acanthosis nigricans, despite attempts at ap- propriate lifestyle changes. Obesity and insulin resistance in the peripubertal child and adolescent can be frustrating to manage for the child, their family, and their health care workers because entrenched unhealthy lifestyle patterns are often compounded by the physiological insulin resistance of puberty.

However, there is little evidence-based information to guide the clinician in the management of insulin resistance in children and adolescents. young individuals with insulin resistance and obesity.

However, we did not find significant differences in the effect of 6 months of treatment with metformin over placebo in any of these parameters.

At the same time, the clinician faced with young patients with insulin resistance and obesity needs treatment options that are safe and effective. Metformin therapy has beneficial effects on body com- Similar to two previous studies assessing the role of metformin in a small number of pediatric subjects with obesity and insulin resistance (11, 12), we found that 6 months of metformin therapy resulted in improvement in anthropometry, fasting serum glucose, and insulin but not insulin sensitivity. Visceral abdominal fat is implicated in the development of insulin resistance in adolescents (24, 25), and loss of visceral, rather than sc, fat in adults has greater metabolic benefits (26).

Therefore, the lack of improvement in insulin sensitivity after 6 months of metformin therapy in our study may reflect inadequate visceral fat loss. Another explanation is the questionable ability of the minimal model technique to detect small changes in insulin sensitivity in severely obese patients (27). Puberty is a time of physiological insulin resistance (28 – 33), and six of the 22 patients underwent a change in their pubertal stage over the course of the study.

Whereas this may have confounded the effect of metformin on insulin sensitivity measures, it is not possible to determine whether insulin resistance may have been worse had the patient not been on metformin. The patient numbers in this study were insufficient to statistically assess the effect of pubertal stage on response to metformin therapy.

The primary mechanism of action of metformin is by sup- pression of hepatic glucose production through activation of the insulin receptor, preferentially through insulin receptor substrate-2 (34, 35). However, whether metformin specifically improves peripheral insulin sensitivity in addition to suppression of hepatic glucose has not been consistently demonstrated in previous clinical studies involving adult patients.

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Some studies using the hyperglycemic clamp method have shown increased Kg, implicating muscle as the main site of metformin action (36), although others have not shown improvement in insulin-mediated Kg (34, 37). We used the minimal model technique of assessing insulin sensitivity because it enables determination of insulin sensitiv- Although 6 months of therapy may not be sufficient to have an impact on visceral adipose tissue loss and insulin sensitivity, ethical considerations and patient participation may make longer-term studies difficult to conduct.

We did not specifically address the role of dietary or exercise interventions, and the combination of lifestyle and pharmacological interventions to reduce the morbidity of high-risk patients needs to be assessed in future studies.

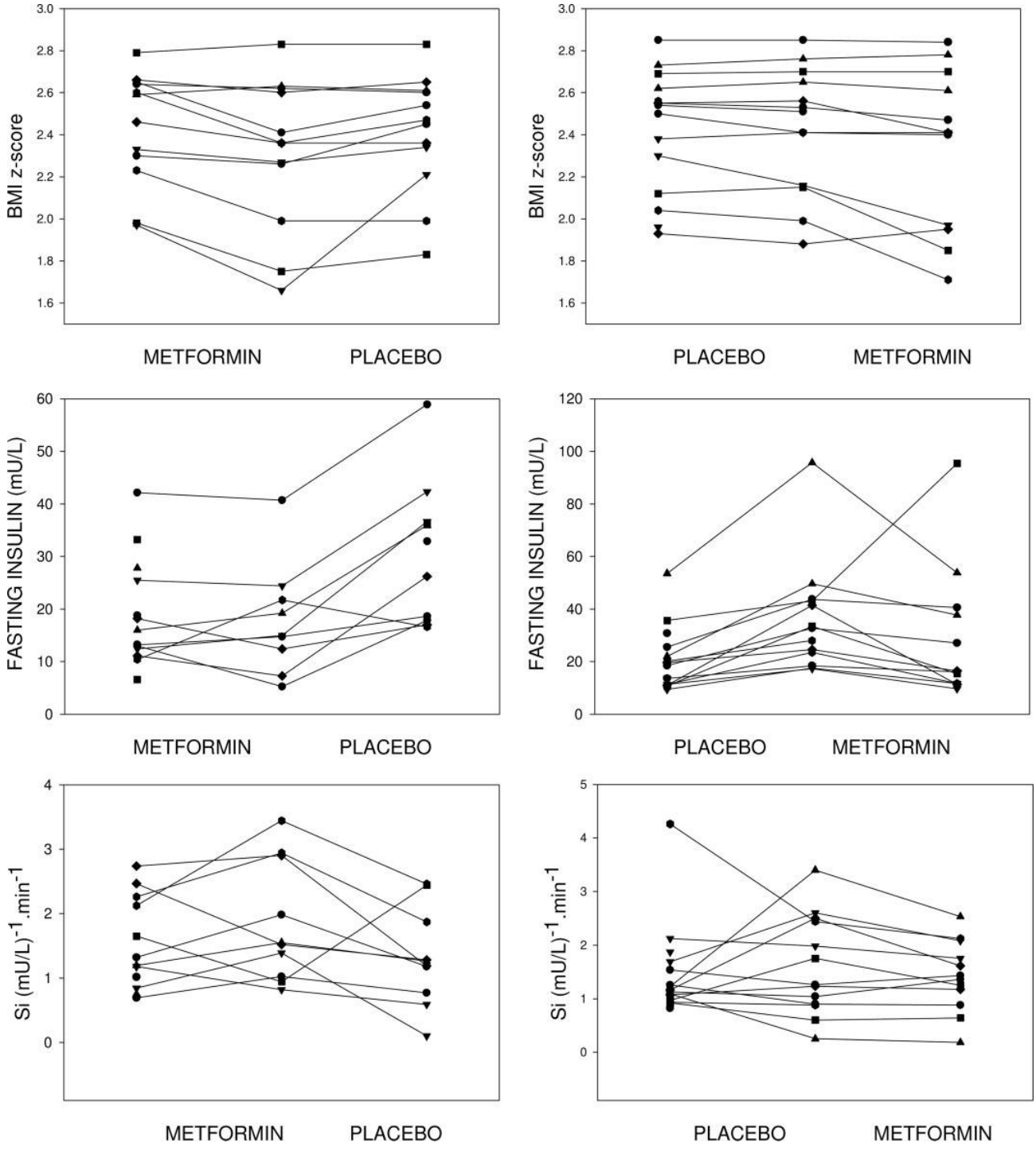

FIG. 3. Metformin and placebo effect on BMI z-score (*top*), fasting insulin (*middle*), and insulin sensitivity (*bottom*).

REFERENCES

[1] **Jones KL, Arslanian S, Peterokova VA, Park JS, Tomlinson MJ** 2002 Effect of metformin in pediatric patients with type 2 diabetes: a randomized con- trolled trial. Diabetes Care 25:89–94

[2] **Hamilton J, Cummings E, Zdravkovic V, Finegood D, Daneman D** 2003 Metformin as an adjunct therapy in adolescents with type 1 diabetes and insulin resistance: a randomized controlled trial. Diabetes Care 26:138–143

[3] **Gomez R, Mokhashi MH, Rao J, Vargas A, Compton T, McCarter R, Chalew SA** 2002 Metformin adjunctive therapy with insulin improves glycemic control in patients with type 1 diabetes mellitus: a pilot study. J Pediatr Endocrinol Metab 15:1147–1151

[4] **Sarnblad S, Kroon M, Aman J** 2003 Metformin as additional therapy in adolescents with poorly controlled type 1 diabetes: randomised placebo-con- trolled trial with aspects on insulin sensitivity. Eur J Endocrinol 149:323–329

[5] **Ibanez L, de Zegher F** 2003 Flutamide-metformin therapy to reduce fat mass in hyperinsulinemic ovarian hyperandrogenism: effects in adolescents and in women on third-generation oral contraception. J Clin Endocrinol Metab 88: 4720–4724

[6] **Ibanez L, Ong K, Ferrer A, Amin R, Dunger D, de Zegher F** 2003 Low-dose flutamide-metformin therapy reverses insulin resistance and reduces fat mass in nonobese adolescents with ovarian hyperandrogenism. J Clin Endocrinol Metab 88:2600–2606

[7] **Arslanian SA, Lewy V, Danadian K, Saad R** 2002 Metformin therapy in obese adolescents with polycystic ovary syndrome and impaired glucose tolerance: amelioration of exaggerated adrenal response to adrenocorticotropin with reduction of insulinemia/insulin resistance. J Clin Endocrinol Metab 87:1555– 1559

[8] **Ibanez L, Valls C, Marcos MV, Ong K, Dunger DB, de Zegher F** 2004 Insulin sensitization for girls with precocious pubarche and with risk for polycystic ovary syndrome: effects of prepubertal initiation and postpubertal discontin- uation of metformin treatment. J Clin Endocrinol Metab 89:4331–4337

[9] **Schwimmer JB, Middleton MS, Deutsch R, Lavine JE** 2005 A phase 2 clinical trial of metformin as a treatment for non-diabetic paediatric non-alcoholic steatohepatitis. Aliment Pharmacol Ther 21:871–879

[10] **Lutjens A, Smit JL** 1977 Effect of biguanide treatment in obese children. Helv Paediatr Acta 31:473–480

[11] **Kay JP, Alemzadeh R, Langley G, D'Angelo L, Smith P, Holshouser S** 2001 Beneficial effects of metformin in normoglycemic morbidly obese adolescents. Metabolism 50:1457–1461

[12] **Freemark M, Bursey D** 2001 The effects of metformin on body mass index and glucose tolerance in obese adolescents with fasting hyperinsulinemia and a family history of type 2 diabetes. Pediatrics 107:E55

[13] **Morrison JA, Cottingham EM, Barton BA** 2002 Metformin for weight loss in pediatric patients taking psychotropic drugs. Am J Psychiatry 159:655–657

[14] **Cole TJ, Bellizzi MC, Flegal KM, Dietz WH** 2000 Establishing a standard definition for child overweight and obesity worldwide: international survey. BMJ 320:1240–1243

[15] **Quon MJ** 2001 Limitations of the fasting glucose to insulin ratio as an index of insulin sensitivity. J Clin Endocrinol Metab 86:4615–4617

[16] 2005 CDC growth charts for the United States. Methods and Development. www.cdc.gov/nchs/data/series/sr_11/sr11_246.pdf. Accessed April 2005

[17] **Fernandez JR, Redden DT, Pietrobelli A, Allison DB** 2004 Waist circumfer- ence percentiles in nationally representative samples of African-American, European-American, and Mexican-American children and adolescents. J Pe- diatr 145:439–444

[18] **Tanner JM, Whitehouse RH** 1976 Clinical longitudinal standards for height, weight, height velocity, weight velocity, and stages of puberty. Arch Dis Child 51:170–179

[19] **Burke JP, Hale DE, Hazuda HP, Stern MP** 1999 A quantitative scale of acanthosis nigricans. Diabetes Care 22:1655–1659

[20] **Bergman RN, Ider YZ, Bowden CR, Cobelli C** 1979 Quantitative estimation of insulin sensitivity. Am J Physiol 236:E667–E677

[21] **Pocock S** 1983 Crossover trials. Clinical trials: a practical approach. Chichester, NY: John Wiley and Sons; 110–122

[22] **Garber AJ** 2000 Using dose-response characteristics of therapeutics agents for treatment decisions in type 2 diabetes. Diabetes Obes Metab 2:139–147

[23] **Osterberg L, Blaschke T** 2005 Adherence to medication. N Engl J Med 353: 487–497

[24] **Weiss R, Taksali SE, Dufour S, Yeckel CW, Papademetris X, Cline G, Tam- borlane WV, Dziura J, Shulman GI, Caprio S** 2005 The "obese insulin-sensitive" adolescent: importance of adiponectin and lipid partitioning. J Clin Endocrinol Metab 90:3731–3737

[25] **Rodriguez G, Moreno LA, Blay MG, Blay VA, Garagorri JM, Sarria A, Bueno**

[26] **M** 2004 Body composition in adolescents: measurements and metabolic as- pects. Int J Obes Relat Metab Disord 28(Suppl 3):S54–S58

[27] **Park HS, Lee K** 2005 Greater beneficial effects of visceral fat reduction com- pared with subcutaneous fat reduction on parameters of the metabolic syn- drome: a study of weight reduction programmes in subjects with visceral and subcutaneous obesity. Diabet Med 22:266–272

[28] **Monzillo LU, Hamdy O** 2003 Evaluation of insulin sensitivity in clinical practice and in research settings. Nutr Rev 61:397–412

[29] **Grant DB** 1967 Fasting serum insulin levels in childhood. Arch Dis Child 42:375–378

[30] **Bloch CA, Clemons P, Sperling MA** 1987 Puberty decreases insulin sensi- tivity. J Pediatr 110:481–487

[31] **Travers SH, Jeffers BW, Bloch CA, Hill JO, Eckel RH** 1995 Gender and Tanner stage differences in body composition and insulin sensitivity in early pubertal children. J Clin Endocrinol Metab 80:172–178

[32] **Goran MI, Gower BA** 2001 Longitudinal study on pubertal insulin resistance. Diabetes 50:2444–2450

[33] **Moran A, Jacobs Jr DR, Steinberger J, Hong CP, Prineas R, Luepker R, Sinaiko AR** 1999 Insulin resistance during puberty: results from clamp studies in 357 children. Diabetes 48:2039–2044

[34] **Caprio S, Plewe G, Diamond MP, Simonson DC, Boulware SD, Sherwin RS, Tamborlane WV** 1989 Increased insulin secretion in puberty: a compensatory response to reductions in insulin sensitivity. J Pediatr 114:963–967

[35] **Cusi K, Consoli A, DeFronzo RA** 1996 Metabolic effects of metformin on glucose and lactate metabolism in noninsulin-dependent diabetes mellitus. J Clin Endocrinol Metab 81:4059–4067

[36] **Gunton JE, Delhanty PJ, Takahashi S, Baxter RC** 2003 Metformin rapidly increases insulin receptor activation in human liver and signals preferentially through insulin-receptor substrate-2. J Clin Endocrinol Metab 88:1323–1332

[37] **Bailey CJ, Turner RC** 1996 Metformin. N Engl J Med 334:574–579

[38] **Perriello G, Misericordia P, Volpi E, Santucci A, Santucci C, Ferrannini E, Ventura MM, Santeusanio F, Brunetti P, Bolli GB** 1994 Acute antihypergly- cemic mechanisms of metformin in NIDDM. Evidence for suppression of lipid oxidation and hepatic glucose production. Diabetes 43:920–928

[39] **Ibanez L, de Zegher F** 2005 Flutamide-metformin plus ethinylestradiol-dro- spirenone for lipolysis and antiatherogenesis in young women with ovarian hyperandrogenism: the key role of metformin at the start and after more than one year of therapy. J Clin Endocrinol Metab 90:39–43

[40] **Ibanez L, Fucci A, Valls C, Ong K, Dunger D, de Zegher F** 2005 Neutrophil count in small-for-gestational age children: contrasting effects of metformin and growth hormone therapy. J Clin Endocrinol Metab 90:3435–3439

[41] **Boston RC, Stefanovski D, Moate PJ, Sumner AE, Watanabe RM, Bergman RN** 2003 MINMOD Millenium: a computer program to calculate glucose effectiveness and insulin sensitivity from the frequently sampled intravenous glucose tolerance test. Diabetes Technol Ther 5:1003–1015