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ADDITION OF METFORMIN TO A LIFESTYLE MODIFICATION PROGRAM IN ADOLESCENT WITH INSULIN RESISTANCE

Kathy Love-Osborne, MD [principal investigator and corresponding author Assistant Professor, Director],
Division of Adolescent Medicine, Department of Pediatrics, University of Colorado at Denver and Health Sciences Center, Denver CO

Eastside Teen Clinic, Denver Health and Hospitals, 501 28th St. Denver, CO 80205, Office: (303) 436-4688. Fax: (303) 436-4665., Email: kathryn.love-osborne@dhha.org

Jeanelle Sheeder, MSPH, and
University of Colorado at Denver and Health Sciences Center, Denver CO

Phil Zeitler, MD, PhD [Associate Professor]
Division of Endocrinology, Department of Pediatrics and Barbara Davis Center for Childhood Diabetes, University of Colorado at Denver and Health Sciences Center, Denver CO

Abstract

Objective—To evaluate whether metformin, when added to a program of personal goal setting, improves weight loss and clinical status in obese adolescents.

Study design—In a randomized double-blind placebo controlled trial, 85 adolescents with insulin-resistance were randomized to receive metformin (70%) or placebo (30%), along with monthly goal setting for diet and exercise modification. Anthropometric measures, fasting blood analysis, and glucose tolerance tests were performed at baseline and 6 months.

Results—Mean age was 15.7 years. Mean body mass index (BMI) was 39.7 kg/m2. 71% were female, 58% Hispanic, and 34% African-American (AA). 76% of participants completed the study. Goal setting alone did not result in significant weight loss. In addition, there were no group differences between metformin and placebo in weight loss or measures of glucose metabolism. However, among females taking metformin, there was a significant decrease in BMI not seen in the placebo group. Furthermore, metformin adherence, when accompanied by lifestyle change, was a predictor of BMI decrease of 5% or more. 60% of 10 subjects who adhered to metformin and decreased portion size decreased BMI by > 5%.

Conclusions—In this group of predominately minority adolescents, monthly goal setting alone did not lead to weight loss. Although the addition of metformin had no effect on weight loss overall, the agent did significantly increase weight loss among females and weight loss was predicted by degree of metformin adherence. However, weight loss was only found in those participants also reporting lifestyle change, particularly a decrease in portion sizes. These results suggest that

Reprint requests: kathryn.love-osborne@dhha.org

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metformin may be a useful agent to promote short-term weight loss among girls making modest lifestyle changes.

As obesity has become more prevalent, the incidence of type 2 diabetes mellitus (T2DM) and other obesity-related co-morbidities in adolescents have increased dramatically. [1] The increase in obesity has been linked to changes in physical activity and intake of calorie-dense foods, such as fast-food and sugared drinks. [2] Early onset T2DM disproportionately affects racial and ethnic minorities. Within populations at high-risk for development of T2DM, subjects with insulin resistance are at particularly high risk for progression to diabetes. In a study of Australian youth (ages 8–29), subjects who developed IGT or T2DM at follow up 7–12 years later had elevated fasting and 2-hour insulin levels at baseline. [3]

The rate of progression from impaired glucose tolerance (IGT, 2-hour glucose 140–199 mg/dl) to T2DM in adults depends on change in weight over time, with reversal of IGT to NGT predicted by the ability to avoid weight gain with aging. [4] Among first degree relatives of T2DM patients, subjects that developed T2DM 5–8 years later gained 5–10 kg, whereas subjects with continued NGT maintained or lost weight. Thus, a modest goal of arresting weight gain may lower the risk of progression to T2DM in susceptible individuals. [5] Even though goal setting techniques have not been extensively studied in adolescents, exercise and healthy diet are effective tools for promoting behavior change in adults. [6] A study of adults with IGT demonstrated that subjects who were successful in attaining at least 4 of 5 goals (weight reduction > 5%, reduced fat and saturated fat intake, increased fiber intake, and exercise > 4 hours/week) did not develop diabetes within 6 years, whereas subjects who were unable to make any lifestyle changes had a 35% incidence of diabetes. [7]

Despite their documented efficacy, the benefits of lifestyle change are difficult to sustain due to poor patient adherence, therefore, alternative treatment options have been sought. In The Diabetes Prevention Program (DPP), while lifestyle modification was more effective than metformin overall in preventing progression to diabetes, the advantage of lifestyle over metformin was less in younger persons and those with a higher body-mass index (BMI). [8] The combination of metformin and lifestyle modification was not explored in this study. Studies on the use of metformin in children and adolescents have been small, but promising. A placebo controlled study of 24 obese Caucasian adolescents evaluating metformin in addition to a hypocaloric diet showed improvement in weight loss and fasting insulin. [9] A study of 29 adolescents with obesity, elevated fasting insulin and a family history of T2DM showed mild improvement in BMI and improvement in fasting glucose and insulin levels. [10]

METHODS

Adolescents ages 12–19 years were recruited through posted advertisements or through contact with primary care providers. Interested participants were invited to a screening visit at which time a family history, physical exam, and fasting laboratory evaluation were obtained. Participants who had fasting insulin level >25 microunits/ml or HOMA (Homeostasis model assessment: fasting insulin in microunits/ml × fasting glucose in millimoles/liter/22.5) > 3.5 and 2 out of 3 risk factors (presence of acanthosis nigricans, obesity (BMI >95% for age), or family history of T2DM) were invited to participate in the study. Exclusion criteria included pre-existing diabetes, pregnancy, heart disease, serum gamma-glutamyl transferase (GGT) over 1.5 times the upper limit of normal, or creatinine > 1.5 mg/dl.

We utilized a randomized, placebo controlled double blind design. The protocol was approved by the Colorado Multiple Institutional Review Board (COMIRB). Eligible subjects were invited to the Pediatric (Clinical Translational Research Center CTRC) at the Children's Hospital in Denver, CO after an overnight fast of at least 10 hours. At this first visit, samples

were drawn for insulin, glucose, lipid panel [cholesterol, high density lipoprotein (HDL), low density lipoprotein (LDL), and triglycerides], creatinine, and GGT or (in the last 50 subjects) aspartate aminotransferase (AST) and alanine aminotransferase (ALT). Female subjects not practicing adequate contraception had a urine pregnancy test. Age, race, BMI, blood pressure (BP), sexual history, alcohol consumption, exercise history, and family history of diabetes were recorded. Subjects then underwent a 2-hour oral glucose tolerance test with a 75 gram glucose load.

Subjects completed a food frequency questionnaire and received written information about symptoms of diabetes from a study physician. They watched a video that emphasized modest calorie reduction, decreased fat and simple sugar consumption, increased fiber, fruit and vegetable intake, and regular aerobic exercise. Subjects then worked with a dietician or study investigator to choose 3 goals for themselves, related to dietary or exercise changes. They were assisted in choosing very specific goals that were attainable in a 1-month period, for example decreasing soda intake from 3 daily to 1 daily. All subjects were encouraged to choose at least one goal related to exercise. They were given a calendar and instructed to record progress on their goals and record if they took the medication.

Upon completion of the baseline visit, subjects were randomized 2:1 by the CTRC pharmacist to receive metformin or placebo. Randomization was stratified by race (AA or other) and fasting insulin level (greater than or less than 40 IU/ml). Subjects were started on metformin or placebo 500 mg once daily. At one month, the dose increased to 500 mg twice daily, followed by an increase to 850 mg twice daily at 2 months. If gastrointestinal side effects persisted for more than 2 weeks, the dose was lowered to the previously tolerated dose.

Subjects were seen monthly for measurement of weight and BP, urine pregnancy test if indicated, assessment of adherence to goals, contraception, alcohol consumption, and adherence with and tolerability of treatment. The research assistant met subjects at a convenient location chosen by the subject; the only requirement being the presence of a scale. The majority of follow-up visits were conducted at schools. A pill count was to be completed at each visit; however, most pill counts were estimated by subjects, as they were unable to carry medications at school. In this population of largely indigent patients followed at school-based health centers subjects were considered adherent if 4 or more medication bottles were dispensed over the 6^{th} month study. With this cut-off, subjects should have taken the maximum dose of metformin for at least 2 months. Subjects were allowed to modify their personal goals at each visit. The research assistant was trained by the study dietician to assess whether subjects had been adherent with their goals and to encourage change to more or less difficult goals if necessary.

At 6 months, the subjects returned to the Pediatric CTRC after a 10 hour fast. Outcome measures obtained included fasting insulin, fasting and 2-hour glucose, lipid panel, BMI, and BP. Subjects again completed a food frequency questionnaire. Subjects were also interviewed regarding lifestyle changes they had made during the 6-month study period. The interview was conducted in a motivational style to promote continued healthy lifestyle changes by an interviewer unaware of group assignment. Responses per subject could be multiple. Subject responses were grouped into categories based on similar themes.

All laboratory assays, except serum insulin, were performed by standard clinical laboratory procedure at the Children's Hospital in Denver. Insulin assay was performed by microparticle enzyme immunoassay (Diagnostic Systems Lab) at the Core Laboratory of the General Clinical Research Center at the University of Colorado at Denver and Health Sciences Center. The sensitivity of the assay is 3 microunits/ml . Within day precision is 5.2 microunits/ml; between-day precision is 9.8 microunits/ml.

T-tests and stepwise logistic regression analysis were performed to analyze the relationship between selected variables (sex, medication group, and specific goal type including increase in exercise, decrease in portion size, increase in positive dietary choices, and decrease in negative dietary choices) to a decrease in BMI of >5% or more. All statistical analyses were performed using SPSS/PC (version 14; 2006[H1]).

RESULTS

85 subjects were enrolled (Table I). The mean age was 15.7 years (range 12–19 years) and mean BMI 39.7 kg/m2 (range 28–55). 71% of the subjects were female. 58% Hispanic, 34% AA. 80% of metformin subjects and 64% of placebo subjects completed the 6-month visit (NS). 50% of metformin and 48% of placebo subjects completed at least 5 of 7 possible visits. There were no differences in sex, BMI, or change in weight at last visit between participants in the metformin and placebo groups dropping out of the study before the 6-month visit.

Medication adherence

Good adherence was demonstrated by 60% and 75% of subjects on metformin and placebo, respectively (NS). 14 subjects on metformin (29%) reported gastrointestinal side effects compared with 3 subjects on placebo (19%). 47% reporting side effects had good pill adherence vs. 68% without reported side effects. Of the 21 subjects who dropped out, 3 reported gastrointestinal side effects as the reason; 2 on metformin and 1 on placebo.

Lifestyle modification

60 subjects (94% of study completers) had interview information available from the 6-month visit. Responses for goal setting were categorized into 4 positive areas: increase in positive dietary change such as more fruits, vegetables, or water (N = 19); decrease in negative dietary choices such as less fast food, junk food, or soda (N = 29); more exercise (N = 36); or smaller portions (N = 18). Negative responses such as no changes made, not exercising, and larger portions were combined into one group (N = 13).

Weight loss

Goal setting alone did not lead to weight loss in this group of adolescents. There was no overall difference in weight loss between subjects receiving metformin or placebo (Table II). However, 11 (23%) subjects on metformin and no subjects on placebo had a BMI decrease of 5% or more. Of subjects that dropped out after only one off-site visit and had no further follow-up (N = 6, 4 metformin and 2 placebo), only one subject had lost weight (mean + .9 kg). That subject was taking metformin.

Subjects adherent with metformin (N = 30) decreased BMI to the greatest extent, though subjects with lower adherence to metformin (3 or fewer bottles) gained less weight than adherent subjects on placebo (0.1 kg/m2 vs. 0.63 kg/m2). Of subjects on metformin with good medication adherence, 8 (27%) attained BMI decrease of 5%. Among those who took all 6 bottles of metformin (N = 14), 5 (36%) decreased BMI by 5%.

Sex differences—The mean change in BMI for female subjects on metformin (N = 33) was −0.40 kg/m2 ± 1.60 compared with 1.04 kg/m2 ± 1.19 for females on placebo (N = 9), (p = .02). For males, the mean change in BMI on metformin (N = 15) was −0.35 kg/m2 ± 2.69 compared with 0.34 kg/m2 ± 1.20 on placebo (N = 7), (NS) Females were twice as likely as males to decrease their BMI by 5% or more (p = .002); of the 11 subjects decreasing BMI at least 5%, 9 were female. Among female subjects with good metformin adherence, only 10% gained weight, compared with 50% of male subjects. These differences were not explained by difference in adherence.

Lifestyle-medication interactions (Table III)—[H2]Subjects who reported a decrease in portion size and were also adherent with metformin (N = 10) lost significantly more weight (BMI −1.3 kg/m2, p = .005) than adherent subjects not reporting decreased portion size, non adherent subjects irrespective of change in portion size, and all placebo groups (BMI +.4 kg/m2 for all other groups). Strikingly, 60% of metformin adherent subjects who reported decreased portion size were able to decrease BMI by 5%. (p = .02). Subjects on metformin reporting a decrease in negative dietary choices (N = 21) showed a trend towards weight loss that did not reach statistical significance (−.61 kg/m2, p = .08). Increase in healthy foods and increase in exercise were not associated with BMI decrease.

Twelve girls (28%) on metformin and 4 (24%) on placebo reported a decrease in portion size at the end of the 6-month study compared to 1 boy (6%) on metformin and 1 (12%) on placebo. In logistic regression, medication group and portion size proved to be significant predictors of a decrease in BMI > 5%. However, when sex was added, medication group and sex were significant predictors, but not portion size.

Laboratory values

Baseline laboratory values are shown in Table I. 10 subjects (15.6%) had abnormal glucose at baseline: 3 (4.7%) IFG, 4 (6.3%) IGT and 3 with both IFG and IGT (4.7%). No subject had overt diabetes at baseline or during the 6-month study period. Seven had worsening IGT (N = 2) or developed IFG or IGT (N = 5), and 6 subjects had resolution or improvement of IFG or IGT.

There were no statistical differences in the change of laboratory values at 6 months between subjects receiving metformin and placebo. However, a decrease in BMI of 5% or greater was associated with a mean improvement in 2-hour glucose concentration of 11.6 mg/dl (p = .03). Subjects with baseline IFG, IGT or IFG/ IGT were more likely to improve if they lost weight; of 10 subjects with abnormal glucose at baseline, the 6 subjects that resolved or improved decreased BMI by a mean of 1.3 kg/m2. Of 7 subjects that had development or worsening of IGT, 5 had gained weight, with a mean BMI increase of .5 kg/m2.

DISCUSSION

As a group, subjects taking metformin did not lose more weight than those taking placebo, indicating that metformin is not, by itself, a robust promoter of weight loss. Indeed, some subjects with good adherence to metformin, particularly among the boys, gained weight, indicating that metformin alone does not necessarily lead to weight loss. However, in these obese, predominately minority adolescents with insulin-resistance, all subjects who lost a clinically significant amount of weight were taking metformin. 36% of subjects with excellent metformin adherence and 23% of those with good metformin adherence were able to attain a BMI loss of 5% or more, compared with no subjects on placebo. Among subjects reporting decreased portion size, those taking metformin were more likely to lose weight: 70% of metformin adherent subjects compared with only 20% of placebo adherent subjects. Weight loss also correlated linearly with metformin adherence; subjects with excellent adherence with metformin were most likely to decrease BMI by 5%, followed by those with moderate adherence, those with less than desirable adherence, followed by subjects on placebo with good adherence, with non-adherent placebo subjects gaining the most weight.

There were sex differences in response to metformin. Girls taking metformin had a significant decrease in BMI compared with placebo, although this was not seen among the male participants. Furthermore, girls were twice as likely as boys to decrease their BMI by 5%, and were less likely to gain weight than boys. The reasons for the sex difference in response to metformin are not clear. This may represent true sex differences in the action of metformin or

underlying differences in mechanism or degree of insulin resistance. Alternatively, girls were more likely to report a decrease in portion size than boys, whether they were taking metformin or placebo. Given the apparent interaction between portion size change and weight loss with metformin on the one hand and the interaction between sex and decreased portion size on the other, the difference in reported lifestyle changes may account for the higher frequency of successful weight loss in girls. However, the relatively small number of boys in the study may obscure the results because boys did show a trend towards improved weight with medication, although less impressive than in girls.

Previous attempts at lifestyle modification in the research setting have been very intensive (usually 2–4 times a month) and costly [11], and would be difficult to replicate in a practice setting. The type of lifestyle modification program used here- personal goal setting- can be replicated in primary care. In this study, subjects almost universally felt that goal setting was helpful to them, regardless of outcome. Subjects who were able to decrease their BMI by 5% (all on metformin) reported having decreased portion size and showed a trend towards decreased negative dietary choices such as soda, junk food, or fast food. A larger sample size might have demonstrated a decrease in negative food choices to be statistically significant.

There are a number of limitations to this study. Subjects that dropped out of the study after the first off-site visit had almost universally gained weight, whether they were on metformin or placebo. If placebo subjects were more likely to drop out because of failure to lose weight in the program, the difference in weight loss between the two groups may have been greater. However, the distribution of drop-outs between the metformin and placebo groups does not indicate that the weight loss seen in the two groups would have been substantially altered. In subjects that did not complete the 6-month visit but had at least one off-site visit, most subjects had gained weight, implying that lack of success with weight loss may have led to early discontinuation of the study in a significant subset of subjects. This effect was seen both in subjects on placebo and on metformin. The rate of dropouts does suggest that many adolescents will not continue with a program that does not show rapid results. The drop-out rate was higher (although not statistically significant) in placebo subjects, which led to lower numbers of placebo subjects in the final analysis. However, there were more placebo than metformin subjects that completed multiple off-site visits but did not complete the 6-month visit, indicating that the overall participation in the study between the groups was similar.

The weights at intermediate visits were not analyzed because off-site weights were not on calibrated scales and heights were not obtained at these intermediate visits. There were subjects that had not taken metformin for several months prior to the 6-month visit. Some subjects may have lost more weight at an intermediate point in the study. Using only the 6-month measurements may have underestimated maximum weight loss in some subjects.

The dose of metformin was escalated slowly, with the maximum dose of medication not reached until the 3rd visit (2 months after initiation of the study). If subjects receiving metformin who dropped out early had received higher doses of metformin sooner, they may have been less likely to drop out. Furthermore, because initial weight loss is likely to reinforce positive lifestyle change, more rapid escalation of dose and/or higher maximum dose might have resulted in larger difference in weight loss between the metformin and placebo groups.

The relatively small number of subjects may have influenced the lack of observed benefit in laboratory values. Furthermore, the study group was composed of mostly Hispanic and African- American adolescents with elevated fasting insulin levels and severe obesity. The outcomes may be different in patients of other racial and ethnic background with varying degrees of insulin resistance or obesity. For example, a previous study has shown that metformin is more effective in Caucasian than African- American subjects, [12] and our

population had few Caucasian subjects. Therefore, the effects of metformin efficacy should be studied in larger groups of ethnically diverse adolescents.

Finally, this study examined the use of metformin for only 6 months. Given that the efficacy of many weight loss interventions wanes with time, future research should address whether beneficial effects of metformin persist over a longer period of time, as well as whether any of these effects persist after medication is discontinued.

These results indicate that metformin was beneficial as a weight loss medication in a subset of obese adolescents with insulin resistance. Conversely, personal goal setting alone did not show evidence of substantial benefit, as even subjects with excellent adherence to placebo and personal goal setting sessions were unable to attain significant weight loss. Girls taking metformin had a significant decrease in BMI compared with those taking placebo and were much less likely to gain weight than boys; they were also much more likely to report decrease in portion size. Increasing metformin adherence was associated with a higher likelihood of significant BMI decrease.

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Table 1

Baseline clinical and laboratory values (mean +/− SD) of enrolled subjects

	Metformin N = 60	Placebo N = 25	P-value
Age (years)	15.5 ± 1.7	14.2 ± 4.6	0.18
Sex (% female)	43 (72 %)	17 (68%)	0.74
Race: Hispanic	34 (57%)	14 (52%)	0.70
Race: AA	20 (33%)	9 (36%)	0.82
Race: Other	6 (10%)	2 (8%)	0.78
Family history T2DM	55 (92%)	23 (92%)	NS
BMI (kg/m2)	39.4 ± 6.5	39.3 ± 7.2	0.95
BMI z-score	4.6 ± 1.8	6.2 ± 8.9	0.41
Weight (kg)	108.8 ± 23.1	110.6 ± 23.4	0.74
Systolic BP	130.5 ± 18.7	130.3 ± 16.2	0.97
Diastolic BP	69.4 ± 10.6	70.1 ± 6.9	0.73
Fasting glucose mg/dl	88.5 ± 11.6	88.8 ± 10.0	0.91
2-hour glucose mg/dl	112.1 ± 22.6	110.4 ± 26.4	0.77
Fasting Insulin microunits/ml	35.8 ± 19.4	34.4 ± 14.5	0.74
2-hour Insulin microunits/ml	164.4 ± 119.4	163.0 ± 92.4	0.96
Fasting triglycerides mg/dl	148.0 ± 84.8	138.5 ± 58.2	0.61
IFG only # (%)	5 (8.3%)	2 (6.7%)	0.96
IGT only # (%)	5 (8.3%)	2 (6.7%)	0.96
IFG and IGT # (%)	2 (3.3%)	1 (4%)	0.88

Table 2

Decrease in BMI in study completers: metformin vs. placebo

	Metformin (N= 48)	Placebo (N= 16)	p-value
Mean change in BMI	−0.16 ± 1.89	0.63 ± 1.29	0.11
BMI decrease of > 5%	11(22.9%)	0(0.0%)	**0.001***
Increase in BMI	20 (41.7%)	11 (68.8%)	0.06

Table 3

BMI change by medication adherence category

	Metformin Adherent Decrease portions N= 10	**Metformin Adherent no decrease portions N = 17**	**Metformin non-adherent, Decreased portions N = 3**	**Metformin Non-adherent No decrease Portions N = 15**	**Placebo Adherent Decreased portion N= 5**	**Placebo adherent No decrease Portion N = 5**	**Placebo non-adherent Decreased portion N = 0**	**Placebo non-adherent No decrease portions N = 5**	**Significance**
Mean change in BMI (kg/m2)	−1.3 ± 1.5	0.4 ± 2.1	0.3 ± 0.7	0.1 ± 2.0	0.7 ± 1.0	0.6 ± 1.5		0.7 ± 1.7	F=1.4; **p=0.2**
BMI decrease of > 5%	6 (60.0%)	1 (5.9%)	0 (0.0%)	3 (20.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)	F=4.0; **p=0.02**