Clinical Use of Metformin in Non-Diabetic, Obese, At-Risk Adolescents: A Systematic Review

Regan R. Brown

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Clinical Use of Metformin in Non-Diabetic, Obese, At-Risk Adolescents: A Systematic Review

Abstract

Background: Type 2 diabetes (T2D) is a disease effecting people of every age, ethnicity, and gender and rates of the disease do not appear to be declining in the near future. The road to T2D is characterized by the combination of peripheral insulin resistance and inadequate insulin secretion by pancreatic beta cells. Although the factors that contribute to the development of T2D are complex and not fully elucidated, the triad of severe obesity, hyperinsulinemia, and a family history of T2D is known to place a child at an increased risk for subsequent development of the disease. The purpose of this study is to explore the preventative potential of metformin in obese, non-diabetic adolescents at-risk for the development of T2D.

Methods: An exhaustive search of available medical literature was conducted using Medline-OVID, CINAHL, and Google Scholar using the key words: adolescents, metformin, diabetes – prevention and control, obesity, and diabetic risk factors. Articles with primary data evaluating the use of metformin in obese, non-diabetic adolescents were included. These relevant articles were assessed for quality using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE).

Results: Three studies met the inclusion criteria for this systematic review of literature. A double-blind, placebo-controlled study of the effects of metformin on body mass index and glucose tolerance in 29 obese adolescents with fasting hyperinsulinemia and a family history of type 2 diabetes demonstrated a significant decline in BMI and decreased insulin and glucose concentrations. Another double-blind, placebo-controlled study of metformin in non-diabetic, hyperinsulinemic, obese adolescents maintained on a low-calorie diet demonstrated statistically significant weight loss in the metformin group as well as improved insulin concentrations. Lastly, a randomized double-blind placebo-controlled trial evaluating metformin in addition to personal goal setting with weight loss and clinical status in 85 obese adolescents with insulin resistance demonstrated significant decrease in BMI in females with metformin adherence and lifestyle changes.

Conclusion: Metformin has been demonstrated to aid with weight loss and insulin sensitivity in select obese, non-diabetic adolescents with risk factors for diabetes. The overall combined quality of the studies reviewed is low based on the GRADE criteria. A recommendation for the use of metformin in obese, non-diabetic, at-risk adolescents who are motivated to create lifestyle changes can be given at this time for short term weight loss goals and increasing insulin sensitivity.

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Keywords
Adolescents, metformin, diabetes, obesity, and diabetic risk factors.

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Clinical Use of Metformin in Non-Diabetic, Obese, At-Risk Adolescents: A Systematic Review

Regan Brown

A Clinical Graduate Project Submitted to the Faculty of the
School of Physician Assistant Studies
Pacific University
Hillsboro, OR
For the Masters of Science Degree, August 10, 2013

Faculty Advisor: Professor Sage Davis-Risen
Clinical Graduate Project Coordinator: Annjanette Sommers, PA-C, MS
Biography

Regan Brown was born in the Bay Area of California but grew up in Spokane, WA. He earned his Bachelor of Science degree in Exercise Science at Eastern Washington University. Prior to PA school, he worked 7 years for Costco Wholesale. Previous medical experience includes assisting in an outpatient Physical Therapy and spine rehabilitation clinic in Spokane for 2 years. He and his wife Amy have been married 8 years and take joy in their daughters Kate (3) and Hadley (1). He takes passion in developing his walk with the Lord, loving and spending time with his family, as well as playing sports. Regan is interested in pursuing a medical career as PA in Family Medicine, Endocrinology, or Pediatric Medicine when he has completed school.
Abstract

**Background:** Type 2 diabetes (T2D) is a disease effecting people of every age, ethnicity, and gender and rates of the disease do not appear to be declining in the near future. The road to T2D is characterized by the combination of peripheral insulin resistance and inadequate insulin secretion by pancreatic beta cells. Although the factors that contribute to the development of T2D are complex and not fully elucidated, the triad of severe obesity, hyperinsulinemia, and a family history of T2D is known to place a child at an increased risk for subsequent development of the disease. The purpose of this study is to explore the preventative potential of metformin in obese, non-diabetic adolescents at-risk for the development of T2D.

**Methods:** An exhaustive search of available medical literature was conducted using Medline-OVID, CINAHL, and Google Scholar using the key words: adolescents, metformin, diabetes – prevention and control, obesity, and diabetic risk factors. Articles with primary data evaluating the use of metformin in obese, non-diabetic adolescents were included. These relevant articles were assessed for quality using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE).

**Results:** Three studies met the inclusion criteria for this systematic review of literature. A double-blind, placebo-controlled study of the effects of metformin on body mass index and glucose tolerance in 29 obese adolescents with fasting hyperinsulinemia and a family history of type 2 diabetes demonstrated a significant decline in BMI and decreased insulin and glucose concentrations. Another double-blind, placebo-controlled study of metformin in non-diabetic, hyperinsulinemic, obese adolescents maintained on a low-calorie diet demonstrated statistically significant weight loss in the metformin group as well as improved insulin concentrations. Lastly, a randomized double-blind placebo-controlled trial evaluating metformin in addition to personal goal setting with weight loss and clinical status in 85 obese adolescents with insulin resistance demonstrated significant decrease in BMI in females with metformin adherence and lifestyle changes.

**Conclusion:** Metformin has been demonstrated to aid with weight loss and insulin sensitivity in select obese, non-diabetic adolescents with risk factors for diabetes. The overall combined quality of the studies reviewed is low based on the GRADE criteria. A recommendation for the use of metformin in obese, non-diabetic, at-risk adolescents who are motivated to create lifestyle changes can be given at this time for short term weight loss goals and increasing insulin sensitivity.

**Keywords:** adolescents, metformin, diabetes, obesity, and diabetic risk factors.
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Table I: Characteristics of Reviewed Studies

List of Abbreviations

BMI ........................................................................................................... Body Mass Index
OGTT ........................................................................................................ Oral Glucose Tolerance Test
T2D .......................................................................................................... Type 2 Diabetes
BACKGROUND

Type 2 diabetes (T2D) is a disease effecting people of every age, ethnicity, and gender and rates of the disease do not appear to be declining in the near future. Rates of diabetes are increasing worldwide. The International Diabetes Federation predicts that the number of people living with diabetes will rise from 366 million in 2011 to 552 million by 2030. The culprit of these spiking numbers is largely due to the increased intake of carbohydrate rich foods and sedentary lifestyles leading to obesity. Most commonly, T2D occurs in adults over the age of 40 and rates increase with age. The Center for Disease Control and Prevention (CDC) reports that in 2005-2008, based on fasting glucose or hemoglobin A1c levels, 35% of U.S. adults aged 20 years or older had prediabetes (50% of adults aged 65 years or older). Applying this percentage to the entire U.S. population in 2010 yields an estimated 79 million American adults aged 20 years or older with prediabetes. The CDC also states about 215 000 people younger than 20 years had diabetes (type 1 or type 2) in the United States in 2010. Most of them have type 1 diabetes, but as obesity rates in children continue to soar, T2D is becoming more of a reality in young people. Genetics play a large role as well, 30% of patients have a positive family history of T2D. Also, increased prevalence of T2D is found in patients with the following risk factors: excessive weight (85% of patients), poor physical fitness, and genetic predisposition.

The road to T2D is characterized by the combination of peripheral insulin resistance and inadequate insulin secretion by pancreatic beta cells. For type 2 diabetes
mellitus to occur, both insulin resistance and inadequate insulin secretion must exist. For example, all overweight individuals have insulin resistance, but diabetes develops only in those who cannot increase insulin secretion sufficiently to compensate for their insulin resistance. Their insulin concentrations may be high, yet inappropriately low for the level of glycemia. In the progression from normal to abnormal glucose tolerance, postprandial blood glucose levels increase first. Eventually, fasting hyperglycemia develops as suppression of hepatic gluconeogenesis fails. Although the factors that contribute to the development of T2D are complex and not fully elucidated, the triad of severe obesity, hyperinsulinemia, and a family history of T2D is known to place a child at an increased risk for subsequent development of the disease.

The prevention of T2D in at-risk adults currently consists mainly of diet and exercise modifications and in some cases the use of metformin. The exact mechanism of action of metformin is unknown, but it has been shown to decrease hepatic glucose production, decrease intestinal absorption of glucose, and improve insulin sensitivity in peripheral tissues. Recently, the Diabetes Prevention Program Outcomes study concluded that in adults, metformin used for diabetes prevention is safe and well tolerated. Weight loss is related to adherence to metformin and is durable for at least 10 years of treatment.

The purpose of this study is to explore the preventative potential of metformin in obese, non-diabetic adolescents at-risk for the development of T2D. This review will primarily be looking at outcomes associated with weight loss and decreasing insulin levels and sensitivity.

METHODS
An exhaustive search of available medical literature was conducted using Medline-OVID, CINAHL, and Google Scholar using the key words: adolescents, metformin, diabetes – prevention and control, obesity, and diabetes risk factors. Articles with primary data evaluating the use of metformin in obese non-diabetic adolescents were included. These relevant articles were assessed for quality using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE).\(^7\)

**RESULTS**

The initial search produced 128 articles for review. After screening of these articles, 3 of these met the inclusion criteria. Each of the 3 were randomized-controlled trials.\(^5,8,9\)

**Freemark and Bursey Study (2001)**

This randomized, double blind, placebo-controlled trial\(^5\) studied the effects of metformin on body mass index (BMI), serum leptin, glucose tolerance, and serum lipids in obese adolescents with fasting hyperinsulinemia and family history of type 2 diabetes. Because the investigation was designed to assess the effects of metformin on glucose tolerance and weight gain in the absence of dietary intervention, the researchers made no attempt to control the caloric intake or food selection of the patients.\(^5\)

A total of 32 patients were enrolled in the study in a randomized, double-blinded manner. All were between 12 and 19 years old and had a BMI exceeding 30 kg/m\(^2\). Criteria for enrollment included: 1) a fasting insulin concentration exceeding 15\(\mu\)U/mL and 2) at least 1, first- or second-degree relative (parent, sibling, or grandparent) with T2D. All patients had normal fasting glucose concentrations (<110 mg%) and HbA1c
concentrations (≤6.0%), and none had glycosuria or ketonuria. The final analysis included data from 14 metformin-treated participants and 15 placebo controls.\textsuperscript{5}

After completing intravenous lab testing and intravenous glucose tolerance test, the patient was discharged with either metformin (500mg) or placebo. Patients were instructed to take one pill at breakfast and one at supper each day. Compliance with the medication was assessed by patient reports and by pill counts at each monthly visit. Because BMI in the normal population varies according to age, gender, and ethnic background, they expressed absolute values of BMI as standard deviation scores (SDS) and changes in BMI as changes in SDS. Changes in insulin sensitivity were assessed by quantifying changes in: 1) the ratio of fasting insulin to glucose concentrations, 2) the quantitative insulin sensitivity check index (QUICKI; 1/[log fasting insulin + log fasting glucose]), and 3) the homeostasis model assessment insulin resistance index (HOMA-IR; fasting insulin × fasting glucose/22.5). QUICKI and HOMA-IR are calculated from the fasting concentrations of glucose and insulin. A P value <.05 was considered statistically significant.\textsuperscript{5}

At baseline, BMI of patients in the metformin treatment group was 7.2% (P < .05) greater than that of patients in the placebo group. There was no statistical difference between groups in baseline plasma glucose or insulin, calculated insulin sensitivity or glucose effectiveness, or HbA1c.\textsuperscript{5}

The authors found that metformin caused a decline of 0.12 SD in BMI during the study, amounting to a mean decrease of 0.5 kg/m\textsuperscript{2}, or -1.3% from baseline. In contrast, BMI rose 0.23 SD, or 2.3% (mean + 0.9 kg/m\textsuperscript{2}) in the placebo group. The differences in absolute and percent change in BMI SDS in the 2 groups were statistically significant (P
Metformin caused a progressive decline in fasting blood glucose levels, from 84 ± 2.2 mg% at the start of the study to 75 ± 1.6 mg% at the end of the 6-month trial (P < .02). In contrast, fasting blood glucose levels in the placebo group did not change significantly during the study. Fasting insulin concentrations in the metformin group declined from 31.5 ± 3.3 µU/mL at baseline to 19.2 ± 1.5 µU/mL after 6 months of treatment (P < .01). In contrast, insulin levels did not change in the placebo group. Lastly, metformin caused a significant (P < .01) albeit small increase in insulin sensitivity as assessed by: 1) the ratio of fasting insulin to glucose concentration, 2) QUICKI, and 3) HOMA-IR.  

Two placebo patients and a metformin-treated patient failed to complete the study for reasons unrelated to drug toxicity or to complications of the trial and were not included in the final analysis.  

The authors found a limitation to this study was due to the small number of patients, therefore, the results must be confirmed in a larger sample. Also, treatment and control groups were not matched precisely for ethnic background, gender, or initial BMI. They discussed the consequences of these differences may have been negated in part because: 1) they expressed the absolute values for BMI as SDS, thereby correcting in part for differences in ethnic background, age, and gender and 2) they expressed changes in BMI in their patients as changes in SDS, and changes in plasma glucose, insulin, leptin, and lipids as a percentage of each individual’s baseline value allowing to use each patient as his or her own control during the study. Next, the study lasted only 6 months and it was discussed whether the positive effects of metformin and drug safety would be sustained over longer periods. Lastly, effects of metformin on BMI and fasting blood
glucose and insulin levels, although statistically significant, were relatively small in magnitude.\textsuperscript{5}

The authors concluded that metformin therapy might complement the effects of dietary and exercise counseling and reduce the risk of type 2 diabetes and can be considered in selected obese adolescent patients with a family history of the disease.\textsuperscript{5}

**Kay et al Study (2001)**

This 8-week randomized, double-blind, placebo-controlled trial\textsuperscript{8} evaluated the anti-obesity effect of metformin in hyperinsulinemic, non-diabetic, obese adolescents. Subjects consisted of 24 Caucasian obese adolescents with a BMI greater than 30 kg/m\textsuperscript{2}. Subjects with a history of glucose intolerance, diabetes, renal disorders, previously identified endocrine disorders, and cardiovascular disease were excluded, as well as those with a fasting glucose greater than 120 mg/dL and/or and HgbA1c \( \geq 7.0\% \). There were no significant differences in age, weight, BMI, or reported caloric intake between the two groups.\textsuperscript{8}

Before beginning the study, all participants were placed on a hypocaloric diet and the placebo medication for a 1-week. This was used as a lead-in period to exclude individuals unlikely to be compliant and ensure a stable body weight before randomization. Subjects were randomly assigned to two, double-blind treatment groups: 12 received metformin for 8 weeks and 12 received a placebo. All subjects were initially started on metformin (850 mg) or placebo once daily. After 1 week, metformin or placebo was increased to twice daily for the remainder of the study. The compliance rates for both groups were comparable. Each subject underwent a comprehensive nutritional evaluation by a registered dietitian and was instructed to complete 24-hour
food records for each of the nine weeks of the study. Before commencing, and after completion of the study, the following laboratory tests were obtained: fasting plasma glucose, insulin, leptin, cholesterol, triglycerides, and free fatty acids (FFA). Glucose-stimulated insulin response and insulin sensitivity were determined both before and after completing the study by an oral glucose tolerance test (OGTT).\textsuperscript{8}

After 8 weeks, some weight loss was observed in both placebo and metformin groups. However, the weight loss was greater in the metformin group (-6.1 ± 0.8 kg) than in the placebo group (-3.2 ± 2.0 kg, \(P < .01\)). There were no significant differences in glucose, insulin, leptin, and lipids between the 2 groups at the beginning of the study. After treatment, the decrease in fasting insulin (\(P < .025\)) was greater in the metformin group than in the placebo group, without a significant change in fasting glucose. Metformin treatment resulted in a marked decrease in the areas under the curve (AUCs) for insulin as compared with control subjects (\(P < .001\)), without a significant change in AUCs for glucose in either group. However, this was associated with a significant increase in the AUC glucose: AUC insulin ratio and the 2-hour glucose: insulin ratio (\(P < .01\)) following metformin treatment without a significant change in the placebo group. Metformin administration caused minimal side effects in five of 12 subjects which resolved.\textsuperscript{8}

The authors admit the limitations of having a small sample size and short duration of the study that larger and long-term studies may be needed to evaluate the metabolic and anti-obesity effects of metformin in hyperinsulinemic, obese adolescents.\textsuperscript{7}

The authors conclude that the present study demonstrated that metformin treatment leads to significant weight loss and decrease in body fat in hyperinsulinemic
obese adolescents. Also this study portrays a significant increase in insulin sensitivity in metformin-treated subjects without a significant change in glycemia and lipid profile in the metformin group. The anti-obesity effect of metformin may be therapeutically beneficial in the management of obese hyperinsulinemic patients.\textsuperscript{8}

**Love-Osborne el al Study (2008)**

In this 6 month randomized, double-blind, placebo-controlled trial\textsuperscript{9}, the authors sought to evaluate whether metformin, when added to a program of personal goal setting, improves weight loss and clinical status in obese adolescents.\textsuperscript{9}

The study consisted of 85 adolescents aged 12-19 years that were invited to a screening visit where a family history, physical exam, and fasting laboratory evaluations were obtained. Participants who had fasting insulin level > 25 microunits/mL or HOMA (Homeostasis mode 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 nigiricans, obesity (BMI > 95% for age), or family history of type 2 diabetes) were invited to participate in the study. At the first visit, baseline labs were drawn, history was taken, and subjects underwent a 2-hour oral glucose tolerance test. Subjects worked with a diettian or study investigator to choose 3 goals for themselves, related to dietary or exercise changes and were instructed to record progress on their goals and whether or not they took the medication on a calendar.\textsuperscript{9}

Subjects were randomized 2:1 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 (500 mg) or placebo 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. 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 the tolerability of treatment.

The authors reported that 85 subjects were enrolled. The mean age was 15.7 years and mean BMI 39.7 kg/m$^2$. Seventy-one percent of the subjects were female. Eighty percent of metformin subjects and sixty-four percent of placebo subjects completed the 6-month visit. Fifty percent of metformin and forty-eight percent of placebo subjects completed at least five of seven possible visits.

Goal setting alone did not lead to weight loss in this group of adolescents. Subjects adherent with metformin (N= 30) decreased BMI to the greatest extent, though subjects with lower adherence to metformin gained less weight than adherent subjects on placebo (0.1 kg/m$^2$ vs. 0.63 kg/m$^2$). 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%. Females were twice as likely as males to decrease their BMI by 5% or more (p = .002). Subjects who reported a decrease in portion size, and were also adherent with metformin (N = 10) lost significantly more weight (BMI -1.3 kg/m$^2$, 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/m$^2$ for all other groups). Strikingly, 60% of metformin adherent subjects who reported decreased portion size were able to decrease BMI by 5% (p = .02). 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).  

The author reported limitations to this study include subjects that dropped out of the study after the first off-site visit had almost universally gained weight, on metformin or placebo. It was discussed that the rate of dropouts may suggest that many adolescents will not continue with a program that does not show rapid results. Also the relatively small number of subjects may have influenced the lack of observed benefit in laboratory values. Finally, this study examined the use of metformin for a period of only 6 months. Discussion that the efficacy of many weight loss interventions wanes with time, therefore future research should address beneficial effects of metformin persist over a longer period of time.  

The authors conclude, the results indicate that metformin was beneficial as a weight loss medication in a subset of obese adolescents with insulin resistance. Girls taking metformin had a significant decrease in BMI compared with those taking placebo and were much less likely to gain weight than boys. Increasing metformin adherence was associated with a higher likelihood of significant BMI decrease as well.  

**DISCUSSION**  

After review of these studies, metformin in the short term can moderately aid in weight loss and insulin sensitivity in obese at-risk adolescents. The outcomes observed and discussed by these three articles suggest weight loss and decreasing insulin levels and resistance to insulin will in turn aid to prevent the eventual progression to type 2 diabetes in select patients. Therefore, the discussion and outcome of most importance is weight loss followed by changes in insulin levels and insulin sensitivity.
Weight Loss

Weight loss or decrease in BMI was observed in all studies that were reviewed. First, Freemark and Bursey\(^5\) observed a mean decrease of 0.5 kg/m\(^2\) in the metformin treatment group while BMI rose by a mean of 0.9 kg/m\(^2\) in the placebo group which was statistically significant. This study was purposely conducted in the absence of dietary intervention. Second, Kay et al\(^8\) evaluated subject’s weight loss on metformin vs placebo in the presence of a low-calorie meal plan (1500 kcal for women and 1800 kcal for men). They observed a statistically significant weight loss greater in the metformin group (-6.1 ± 0.8 kg) than in the placebo group (-3.2 ± 2.0 kg). Finally, Love-Osborne et al\(^9\) evaluated weight loss in subjects along with monthly goal setting for diet and exercise modification. Goal setting alone did not result in significant weight loss. They also found there was no overall difference in weight loss between subjects receiving metformin or placebo. However, 11 subjects on metformin and no subjects on placebo had a BMI decrease of 5% or more. Females on metformin had a mean BMI decrease of the greatest extent.

Insulin Levels/Sensitivity

After reviewing these articles, only 2 out of 3 measured pre and post insulin levels and/or evaluated insulin sensitivity in some fashion. Love-Osborne et al\(^9\) only performed a pre and post oral glucose tolerance test (OGTT) that will be discussed. First, Freemark and Bursey\(^5\) observed statistically significant fasting insulin concentrations in the metformin group declined from 31.5 ± 3.3 µU/mL at baseline to 19.2 ± 1.5 µU/mL after 6 months of treatment. In contrast, fasting insulin levels did not change in the placebo group. Metformin also caused a significant albeit small increase in insulin sensitivity as
assessed by: 1) the ratio of fasting insulin to glucose concentration, 2) QUICKI, and 3) HOMA-IR. Second, Kay et al\textsuperscript{8} displayed a significant decrease in fasting insulin levels in the metformin group (-21 ± 6 µU/mL) in comparison to placebo (-11 ± 5 µU/mL) without a significant change in fasting glucose. Also noted, the areas under the curve (AUCs) as measured by the response to OGTT for insulin decreased with metformin as compared with control subjects (p = .001). Finally, Love-Osborne et al\textsuperscript{9} did not directly observe serum insulin levels, although the authors did perform a pre and post OGTT that revealed a link between weight loss and glucose tolerance. They found 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 (Impaired Fasting Glucose), IGT (Impaired Glucose Tolerance) or IFG/IGT were more likely to improve if they lost weight.

Quality Assessment

All three studies evaluated the outcome of weight loss while only 2 of the 3 looked at the sensitivity of insulin. Following GRADE protocol, all 3 studies being RCTs began with a GRADE of high. Both outcomes, weight loss and insulin sensitivity, were downgraded two levels for lack of precision. These studies admit to being of small sample size and short duration in nature. Overall, the GRADE rating of low was given to both outcomes of weight loss and insulin sensitivity. See Table 1.

CONCLUSION

Metformin has been demonstrated to aid with weight loss and insulin sensitivity in select obese, non-diabetic adolescents with risk factors for diabetes. The results from the studies reviewed emphasize specifically that in combination with either dietary
restriction or setting goals for lifestyle modification, the use of metformin in these adolescents will decrease BMI and serum insulin levels. Also, the only study looking at sex differences pointed out a significant decrease in BMI in females compared to males using metformin. As recommended by the authors of these studies, to evaluate the sustained benefits of metformin there is a need for more long term research with larger sample sizes. The overall combined quality of the studies reviewed is low based on the GRADE criteria. A recommendation for the use of metformin in obese, non-diabetic, at-risk adolescents who are motivated to create lifestyle changes can be given at this time for short term weight loss goals and increasing insulin sensitivity. Further randomized controlled studies evaluating the sustained effects of metformin on the outcomes addressed as well as clinical status, sex differences, and ethnically diverse adolescents will be of great importance.
References


Table I. Characteristics of Reviewed Studies (GRADE TABLE)

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*Small sample size and short duration within each RCT reviewed.