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Effect of Metformin on Adolescent Obesity

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Abstract

Objectives: Metformin is the first line treatment for type 2 diabetes mellitus (T2DM) in both adults and children and has been shown to result in weight loss. Pediatric obesity is a major risk factor for the development of T2DM as well as several other diseases. Recently, physicians have reported using Metformin off-label to treat obesity in adolescent patients. The purpose of this study is to investigate whether Metformin is effective in reducing BMI in obese adolescents.
Methods: Studies were found using PubMed, MeSH, Medline, and CINAHL. The search terms used were: "obesity," Metformin," "adolescents," "children," "metformin and weight," and "metformin and BMI." Several studies were excluded, including meta-analysis studies, reviews, studies written in a foreign language, and studies published before 2000. Studies were also excluded if their sample populations included ages below 6 years old or above 18 years old, if they included participants with T2DM, and studies that involved other drugs besides Metformin. The final 3 studies were chosen based on their relevance to our clinical question.
Results: The first study showed a significant reduction in BMI z score of 0.8 +/-0.2 in prepubertal children, and a nonsignificant reduction of 0.4+/-0.2 in pubertal children. Study 2 showed a significant reduction in BMI-SDS from 3.44 (SD 0.57) to 3.35 (SD 0.65). In Study 3, BMI-SDS was significantly higher in the metformin group compared to the lifestyle intervention group. After 12 months of treatment, this difference disappeared. However, the change in BMI-SDS between the metformin group and lifestyle intervention group in Study 3 was not significant.
Conclusion: Further studies need to be done to determine the role of metformin in treating obese, non-diabetic adolescents. While current studies suggest some benefit of metformin in childhood obesity, sample sizes are relatively low, and results vary between prepubertal and pubertal children. However, our research did show a decrease in standardized BMI in obese pediatric patients receiving metformin, indicating a possible role of metformin in treating adolescent obesity.

Introduction

Pediatric obesity, defined as a BMI equal to or greater than the 95th percentile for age and gender, has been a growing concern worldwide among both resource-rich and resource-poor countries. Among adolescents in the United States, there was a sharp increase in obesity prevalence from 5.0% in 1976 to 20.6% in 2014, highlighting the true extent of the disease and indicating a need for early intervention.[10,12]

Along with upward trends in pediatric obesity, we have seen an increase in associated comorbidities. Diseases such as type 2 diabetes mellitus (T2DM) and fatty liver disease that have long been considered adult diseases are being seen more frequently in pediatric patients. Early onset diabetes markedly increases the risk for developing complications such as retinopathy, neuropathy, nephropathy, and atherosclerotic cardiovascular disease.[6] Adolescent

obesity also poses an increased risk for hypertension, dyslipidemia, cholelithiasis, obstructive sleep apnea, musculoskeletal problems, early onset polycystic ovarian syndrome (PCOS), and premature death in adulthood.[3,4,13,14] Important considerations also include the psychosocial factors of self-esteem, peer relationships, body image, and depression among obese adolescents.

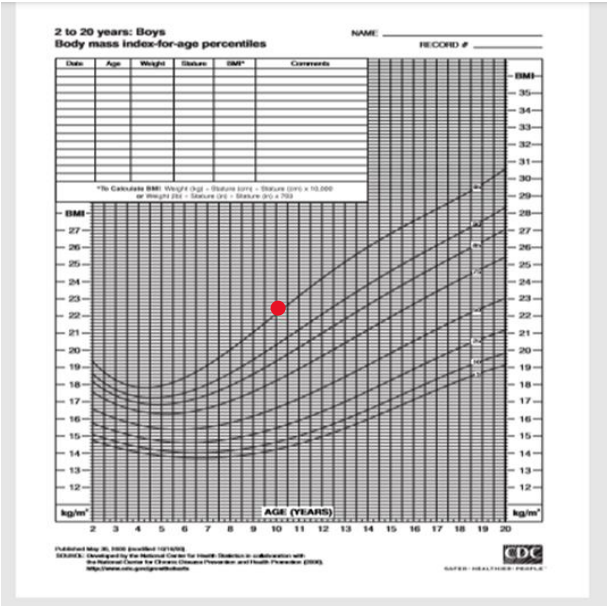
Metformin is the first line treatment for T2DM in adults and adolescents, as it effectively decreases hepatic glucose production and increases insulin sensitivity in peripheral tissues.[2,9] It is relatively well-tolerated, with the most common side effects related to GI disturbances. Along with its benefits of controlling T2DM, metformin has also been shown to cause weight loss.[1,8]

Given its favorable effect on weight, our research focuses on the use of metformin in treating obesity in adolescents. While metformin is approved for treating T2DM in patients 10 years and older, there is limited research on its use for treating childhood obesity. This literature review investigates whether metformin is effective in lowering BMI in obese, non-diabetic adolescents.

Case

J.W. is a 10yo white male presenting to the pediatrician with his parents for concerns regarding his weight. He has a height of 56in and weighs 102 pounds, placing him in the 95th percentile for BMI (figure 1). Both of his parents are overweight and have T2DM. In addition, his grandfather just passed away due to complications from cardiovascular and end stage renal disease as a result of diabetes. J.W.'s parents are worried about their son's health, and previous attempts at diet and exercise modifications have had limited success. His parents also report that J.W. is being bullied at school because of his weight and are concerned for his psychological health. J.W.'s parents are inquiring if there are any medications that could help him lose weight. J.W. himself also seems motivated to lose weight.

Figure 1: J.W.'s height and weight plotted on a pediatric growth curve for boys 2-20yo



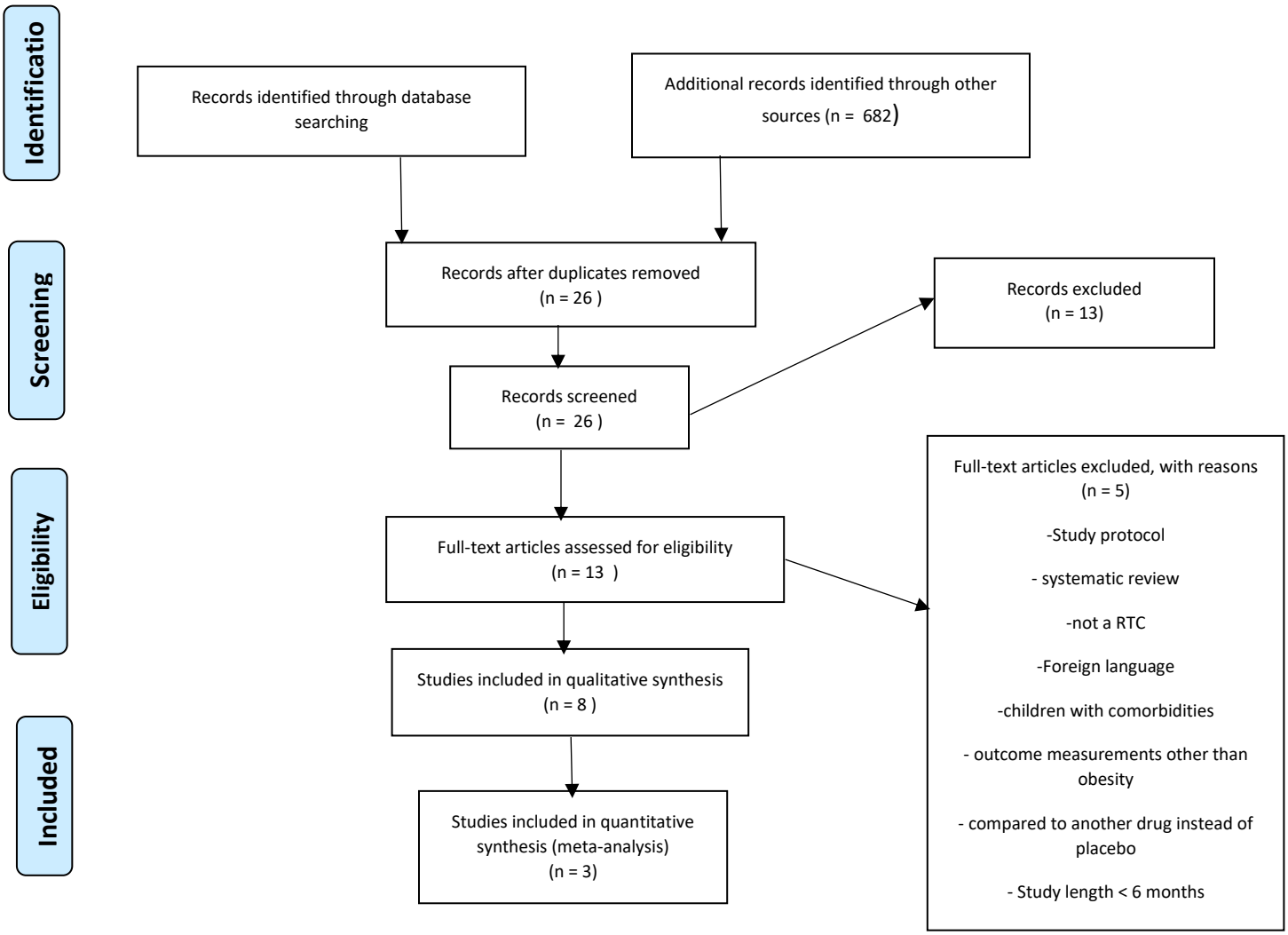
Methods

A database search on PubMed, MeSH, Medline, and CINAHL was performed using the search terms "obesity," "metformin," "adolescents," "children", "metformin and weight," and "metformin and BMI." Filters were implemented to include articles that were published in 2010 or later and were full-text. Initially, articles were excluded if they were meta-analysis studies, reviews, or written in a foreign language. Other exclusion criteria included: Research published before the year 2000, or

studies involving participants with T2DM, subjects younger than 6 or older than 18, girls with obesity and PCOS, and studies investigating antihyperglycemic drugs other than metformin.

Eighty-eight studies on metformin for childhood obesity were identified from the above-mentioned databases using the exclusion criteria. In some cases, further references were identified from reference lists provided by the studies. The searches of electronic databases were supplemented with manual screening of the bibliographies of retrieved publications. The bibliographies of recent systematic reviews and other review articles for potentially relevant citations were also screened. Additional records identified through these other sources summed up to 682 results. All articles identified were subject to the study selection criteria listed above. Upon manual analysis of the articles found, additional exclusions were made by eliminating study protocols, systematic reviews, studies that measured outcomes other than obesity, studies comparing metformin to another drug instead of placebo, or studies with lengths of less than 6 months. Finally, three articles were chosen, two RCT and one retrospective cohort study, as these were studies that best addressed our clinical question.

PRISMA Flow Diagram



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Results

Study #1

Metformin for Obesity in Prepubertal and Pubertal Children: A Randomized Controlled Trial. Pastor-Villaescusa et al.

Study Objective

To determine whether oral metformin treatment reduces BMI-z score, cardiovascular risk, and inflammation biomarkers in children who are obese depending on pubertal stage and sex.

Study Design

The study was conducted as a randomized, double-blind, placebo-controlled trial among 4 Spanish hospitals. The sample population included 160 obese pediatric patients who were referred from Pediatric Endocrinology units and who met the inclusion criteria (Table 1). The subjects were stratified into four groups according to gender and pubertal status (40 prepubertal girls, 40 prepubertal boys, 40 pubertal girls, and 40 pubertal boys). Pubertal status was determined using Tanner criteria.

Inclusion Criteria	Exclusion Criteria
BMI greater than the 95th percentile	Does not meet the established age
Age 7-14	Any previous underlying disease
No underlying disease or a history of pathology	Use of medication with metabolic side effects, such as diuretics, β-blockers, β-adrenergics, or corticoids
No medical treatment regarding weight control in the previous 12 months	Cases of monogenic obesity
No participation in a previous trial	Children subjected to long periods of rest
	Did not sign the informed consent

Table 1: inclusion and exclusion criteria for *Pastor-Villaescusa et al study*

50% of the participants were randomly assigned to metformin and the other 50% to placebo. Each patient was given instructions to take doses during meals, beginning with 50mg twice daily for the first 10 days, and increasing stepwise to 500 mg twice daily until the end of the study. Visits were done at baseline and at 2-month intervals until month 6. All research staff was blinded to treatment allocation.

Outcome measures included anthropometry, blood pressure, serum glucose, serum insulin, hepatic enzymes, and lipids. In addition, the study measured several inflammatory and cardiovascular risk biomarkers. Data analysis was conducted using SPSS software. A Student's t test and Mann-Whitney U test were used to account for differences at baseline for each pubertal/sex group. Bonferroni tests were used to account for specific treatment

differences for the separated groups. Data was not used from subjects who were lost to follow-up.

The study developed a logistic regression model to assess the effect of metformin on BMI z-scores (a numerical measurement of a value's relationship to the mean in a group of values, so if a z-score is 0, it represents the score as identical to the mean score). The odds ratio was reported with 95% confidence intervals.

Study Results

For the purposes of this research, we will be primarily focusing on the BMI z-score results. In the prepubertal group receiving metformin for 6 months, there was a reduction in the BMI z-score by 0.8 +/-0.2. This was statistically significant (P=0.04), as opposed to the placebo group which did not have a statistically significant reduction in BMI z-score. Moreover, the study's binary logistic regression score showed BMI-z scores being independently associated with metformin treatment (OR 0.18 [CI 95%, 0.050-0.636]). The BMI-z score in the pubertal group receiving metformin reduced by 0.4+/-0.2. However, this decrease was not statistically significant, and the placebo group also had no significant reduction in BMI-z score.

Study #2

Metformin in Obese Children and Adolescents: The MOCA trial. Kendall et al.

Study Objective

To assess the effect of metformin on BMI-SDS, metabolic risk factors, and adipokines (cytokines and cell signaling proteins secreted by adipose tissue).

Study Design

The MOCA trial was a multicenter double-blind, placebo-controlled study conducted at six pediatric endocrine centers of the United Kingdom. One hundred fifty-one obese children and young people participated in the study (metformin: 74, placebo: 77). The age range was 8-18 yo, and the mean BMI-SDS was 3.4 (SD 0.5). A positive family history of T2D was recorded in 58.9%.

Participants were placed in 4 stratification groups (males 8-13 yo, females 8-13 yo, males 14-18 yo, and females 14-18 yo). According to a computer-generated randomization list, each stratification group was randomly assigned to receive either 1.5 g of metformin or 1.5 g of placebo (lactose tablet).

All participants were provided with standardized healthy lifestyle advice at the start in a one-to-one session, including a healthy diet advice sheet and increased levels of exercise (available upon request). The participants attended an initial trial baseline visit and then two further visits at 3-month intervals. Every participant had a medical history taken including documentation of a family history of T2D and ethnicity, and a full medical examination was

performed with pubertal assessment. Measurement of arterial blood pressure (BP) and accurate anthropometry including height, weight, and waist and hip measurements were performed at each visit. Other investigations at baseline and at 3 and 6 months included adipokines (e.g. leptin, resistin, adiponectin) and lactate (due to small risk of lactic acidosis).

The main outcome measurement was a reduction in BMI-SDS (standardized BMI) at 6 months. Secondary outcomes included insulin and glucose levels from oral glucose tolerance tests, alanine aminotransferase (ALT), and adiponectin to leptin ratio (ALR) at 3 and 6 months. A standard power calculation was used to detect a reduction in BMI of 0.15 kg/m2 (SD 0.3). Sixty-four participants in each group give a statistical power of 80% for a t test at the 5% significance level.

Study Results

For the purposes of this review, we will be primarily focusing on the BMI-SDS results. Metformin was associated with a significant reduction in BMI-SDS. For the 55 participants in each group, mean BMI-SDS changed from 3.44 (SD 0.57) to 3.35 (0.65) in the metformin group, compared with 3.34 (0.5) to 3.31 (0.54) in the placebo group. The reduction in BMI-SDS in the metformin group compared with placebo was evident at 3 months.

Study #3

Metformin effectiveness and safety in the management of overweight/obese nondiabetic children and adolescents: metabolic benefits of the continuous exposure to metformin at 12 and 24 months. Marques et al.

Study Objective

To evaluate the effectiveness, in terms of weight loss and insulin resistance, and safety of metformin in nondiabetic overweight/obese children and adolescents.

Study Design

This was a retrospective study on overweight/obese nondiabetic children and adolescents followed at Hospital Dona Estefânia in Lisbon, between 2005 and 2013. A total of 78 patients were analyzed. Thirty-nine were treated with metformin, and another 39 patients were randomly selected from the outpatient list of the obesity clinic for the comparison group – lifestyle intervention group (Table 2). All patients were followed by pediatric endocrinologists. Selection criteria included: overweight/obese (BMI≥85th/95th percentile for age and sex, respectively), and ages between 8 and 17 years. The exclusion criteria included: previous diagnosis of diabetes mellitus or use of medication to treat insulin resistance/losing weight, present or past exposure to glucocorticoids, oral contraceptives or any medication that could

interfere with weight, medical disorders predisposing to obesity or insulin resistance such as PCOS, other endocrinopathies or genetic syndromes, and liver or renal dysfunction.
Data from these 78 patients were collected and analyzed at different follow-up periods: baseline, 12 months, and 24 months. Tanner's criteria were used to assess pubertal status.

	Lifestyle intervention (n=39)	Metformin group (n=39)	p-Value
Age, years [range]	12.9 (±2.5) [8.1; 17.4]	13.8 (±1.9) [9.7; 17.0]	0.066
Female sex	19 (48.7%)	22 (56.4%)	0.496
Caucasian ethnicity	39 (100%)	37 (94.9%)	0.358
Family history of obesity	30 (76.9%)	26 (66.7%)	0.314
Family history of T2DM	22 (56.4%)	25 (64.1%)	0.488
Prepubertal status	5 (12.8%)	3 (7.7%)	0.455
Weight, kg	74.6 (±22.4)	93.7 (±17.6)	**0.000**
Height, cm	155.4 (±12.4)	163.5 (±9.6)	**0.002**
Height-SDS	0.3 (±1.2)	0.7 (±1.3)	0.118
BMI, kg/m^2	30.6 (±6.7)	34.9 (±4.8)	**0.002**
BMI-SDS	2.9 (±1.0)	3.3 (±0.8)	**0.038**

Data is shown as mean (±standard deviation) or n (%). T2DM, Type 2 diabetes mellitus; SDS, standard deviation score; BMI, body mass index; HOMA-IR, homeostasis model assessment for insulin-resistance index. Significant differences (p<0.05) in bold.

Table 2: Study population characteristics for Marques et al study.

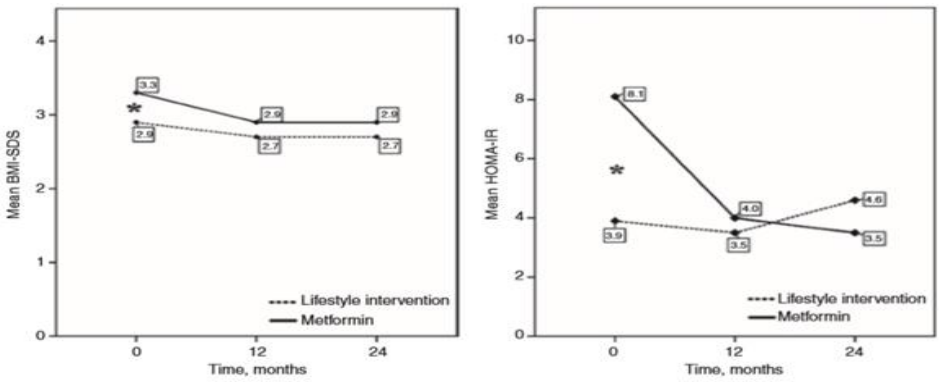
Metformin was initiated in patients with BMI-SDS>2. An initial daily dose of 0.5 g was usually used, with increments to a maximum daily dose of 2 g, based on the clinician's judgment and the patient's tolerance. Both groups were submitted to lifestyle intervention to optimize dietary intake and stimulate physical activity. Dietary and nutritional education was provided by an experienced nutritionist.

Chi-square analysis and Fisher's exact test were used to compare categorical variables. The Student's t-test was used to compare continuous variables; a paired-sample Student's t-test was used to estimate the variable changes at different follow-up times. Results were presented as mean ± standard deviation (SD). A p value <0.05 was considered statistically significant.

Study Results

For the purposes of this review, we will be primarily focusing on the BMI-SDS results. BMI-SDS decreased over time within each group, except for the lifestyle intervention group at 24 months (Figure 2).

Figure 2: Mean BMI and mean insulin resistance at 0, 12, and 24 months



There was a significant difference in BMI-SDS found between metformin and lifestyle intervention groups at baseline (3.3 vs. 2.9; p=0.038), but not at 12 and 24 months. Although ΔBMI-SDS was numerically superior in the metformin group in all periods, there was no statistical significance compared to the lifestyle intervention group.

Critiques and Limitations of Studies

Study 1 was a well-conducted randomized control trial that adjusted their data for differences in baseline BMI. In addition, they stratified their sample population based on pubertal stage. The main limitation in study 1 was the inability to accurately measure intervention compliance to both metformin and lifestyle modifications. In addition, they had a dropout rate of 7.5% in the metformin group and 5% in the placebo group. The data from those that dropped out were excluded from the study's statistical analysis.

Study 2 had a dropout rate of 27%, but they did use an intention-to-treat model for their final analysis to compensate for the high dropout rate. Like study 1, study 2 was also faced with difficulty in assessing compliance with treatment. Furthermore, both study 1 and 2 lacked a lifestyle only arm.

Study 3 had several limitations: small number of patients, high dropout rates at 24 months and discrepancies in the metformin doses. All of these limitations are the result of its retrospective design. However, this study expands the available data on long term (24 mo) metformin effectiveness and safety in pediatric obesity, as the majority of current available research on metformin for pediatric obesity are durations of 6 or 12 months and do not assess the continuous exposure of metformin beyond 12 months.

Discussion

Metformin is FDA approved to treat diabetes type 2 in pediatric patients ages 10 and older. In addition, the drug has been used off-label for weight loss in adults and for prevention of T2DM. Our research suggests metformin may be helpful in treating adolescent obesity, however, subsequent studies are needed to determine this.

Study 1 showed a statistically significant reduction in BMI z score in prepubertal children but not in pubertal children with a 6 month trial of metformin. Physiological and hormonal changes in pubertal children may contribute to this finding. In addition, compliance in prepubertal vs pubertal patients may also play a role. Of note, the study used a lower dose for pubertal children with respect to mg of metformin per kg of body weight. Therefore, further studies should be done to determine the effective dose in pubertal children.

Study 2 showed a small, yet statistically significant, reduction in BMI-SDS in pediatric patients receiving metformin for 6 months compared to their placebo group, which had no mean reduction in BMI-SDS. The study also demonstrated no difference in response to metformin according to pubertal stage, although power of this analysis was low (P=0.79). When interpreting the results of this study, it is important to determine whether a small reduction in BMI-SDS is clinically significant. Some may argue that any reduction is clinically significant as it may serve to reverse a progressive upward trend in an individual's BMI. In addition, a small decrease in BMI may add reinforcement and self-confidence in an adolescent trying to lose weight.

Study 3 was a retrospective study that compared obese adolescents treated with metformin or lifestyle modifications alone. Understandably, the metformin group had a much higher baseline mean BMI. After 12 months, there was no significant difference in BMI-SDS between the metformin group and lifestyle group, indicating a greater change in BMI-SDS in the metformin group. However, the change in BMI-SDS between the two groups was not significantly different. Unlike the other studies included in this research, study 3 observed long term effectiveness of metformin use after 12 and 24 months. The lifestyle only group had significant reduction in BMI-SDS at 12 months but not at 24 months. In contrast, the metformin group had significant BMI-SDS reduction at both 12 and 24 months. This indicates possible long-term benefits of metformin over lifestyle modifications for obese adolescents.

All three studies showed some benefit of metformin for treating childhood obesity. However, the methods of each study varied considerably, which should be considered when analyzing the results of all three studies together. For example, studies 1 and 2 were similar in that they were both randomized control trials that stratified their sample populations based on age and pubertal status. Study 3 did not stratify based on age and pubertal status. However, study 3 is important because it analyzes the long-term effects of metformin on obese adolescents in the clinical setting. Finally, all three studies involved lifestyle modifications in both metformin and non-metformin groups in the form of expert dietary and exercise advice. Since the degree of compliance and homogeneity of these interventions may be hard to analyze, subsequent studies could consider comparing metformin vs placebo without the use of lifestyle modifications.

In addition to reporting changes in standardized BMI, all three studies also analyzed changes in insulin sensitivity and cardiovascular risk biomarkers. All studies reported an improvement in insulin sensitivity or fasting insulin levels, although this finding was limited to

prepubertal children only in study 1. Studies 1 and 2 also reported a significant improvement in adiponectin-leptin ratio with metformin treatment. Study 1 included data on several pro-inflammatory markers and found a decline in plasma INF-y concentration in prepubertal children treated with metformin. On the other hand, no changes were seen in lipid profiles in either group. Study 2 reported additional metabolic risk factors, including ALT which improved in the metformin group at 3 months, but this was not sustained at 6 months. The arterial blood pressure, CRP, lactate, and fasting lipids did not alter significantly during the study. There were no significant changes in adiponectin, resistin, and leptin concentrations. Study 3 also researched safety of metformin in nondiabetic overweight/obese children and adolescents and suggest that metformin may have long-term metabolic benefits, and it appears to be safe in overweight/obese children and adolescents.

Further studies involving larger sample sizes and longer trials should be done to determine the effectiveness and safety of metformin on childhood obesity. Our research indicates a possible benefit of its use in adolescents, but the role of puberty on metformin effectiveness remains unknown. Therefore, further investigation is warranted to determine the role of puberty in obesity treatment.

Case resolution

We believe our research can be applied to J.W., as he would meet the inclusion criteria for all three studies discussed above. Since J.W. has a BMI in the 95th percentile and has a strong family history of diabetes, it may be reasonable to begin Metformin therapy to help reduce his BMI and prevent associated diseases. However, since research regarding long term use of metformin in adolescents is lacking, caution should be taken when considering treatment over 12 months.

Conclusion

In conclusion, further studies need to be done to determine the role of metformin in treating obese, non-diabetic adolescents. While current studies suggest some benefit of metformin on childhood obesity, sample sizes are relatively small, and results vary between prepubertal and pubertal children. In addition, we found no randomized control trials that investigated long term (>6 months) effects of metformin in obese adolescents. Regardless, our research did show a decrease in standardized BMI in obese pediatric patients receiving metformin, indicating a possible role of metformin in treating adolescent obesity.

References

1. Baptista T, Rangel N, Fakih YE, et al. Rosiglitazone in the Assistance of Metabolic Control during Olanzapine Administration in Schizophrenia: A Pilot Double-blind, Placebo-controlled, 12-week Trial. *Pharmacopsychiatry*. 2009;42(01):14-19. doi:10.1055/s-0028-1085438
2. Copeland et al. Clinical Practice Guideline: Management of Newly Diagnosed Type 2 Diabetes Mellitus (T2DM) in Children and Adolescents. Pediatrics. 2013;131(2):364-382. *Pediatrics*. 2013;131(5):1014-1014. doi:10.1542/peds.2013-0666
3. Friesen CA, Roberts CC. Clinical Characteristics in Children. *Clinical Pediatrics*. 1989;28(7):294-298. doi:10.1177/000992288902800701
4. Hannon TS. Childhood Obesity and Type 2 Diabetes Mellitus. *Pediatrics*. 2005;116(2):473-480. doi:10.1542/peds.2004-2536
5. Kendall D, Vail A, Amin R, et al. Metformin in Obese Children and Adolescents: The MOCA Trial. *The Journal of Clinical Endocrinology & Metabolism*. 2013;98(1):322-329. doi:10.1210/jc.2012-2710
6. Magge SN, Goodman E, Armstrong SC. The Metabolic Syndrome in Children and Adolescents: Shifting the Focus to Cardiometabolic Risk Factor Clustering. *Pediatrics*. 2017;140(2). doi:10.1542/peds.2017-1603
7. Marques P, Limbert C, Oliveira L, Santos MI, Lopes L. Metformin effectiveness and safety in the management of overweight/obese nondiabetic children and adolescents: metabolic benefits of the continuous exposure to metformin at 12 and 24 months. *International Journal of Adolescent Medicine and Health*. 2016;29(5). doi:10.1515/ijamh-2015-0110
8. McCulloch DK. Prevention of type 2 diabetes mellitus. Post TW, ed. UpToDate. Waltham, MA: UpToDate Inc. http://www.uptodate.com
9. Nathan DM. Management of Hyperglycemia in Type 2 Diabetes: A Consensus Algorithm for the Initiation and Adjustment of Therapy: A Consensus Statement From the American Diabetes Association and the European Association for the Study of Diabetes: Response to Jellinger, Lebovitz, and Davidson. *Diabetes Care*. 2007;30(4). doi:10.2337/dc06-2600
10. Ogden C, Carroll M. Prevalence of Obesity Among Children and Adolescents: United States, Trends 1963-1965 Through 2007-2008. *PsycEXTRA Dataset*. June 2016. doi:10.1037/e582042012-001
11. Pastor-Villaescusa B, Cañete MD, Villarraso-Caballero J, et al. Metformin for Obesity in Prepubertal and Pubertal Children: A Randomized Controlled Trial.Pediatrics.2017;140 (1):e20164285. *Pediatrics*. 2017;140(5). doi:10.1542/peds.2017-2555
12. Skinner AC, Perrin EM, Skelton JA. Prevalence of obesity and severe obesity in US children, 1999-2014. *Obesity*. 2016;24(5):1116-1123. doi:10.1002/oby.21497
13. Taylor ED. Orthopedic Complications of Overweight in Children and Adolescents. *Pediatrics*. 2006;117(6):2167-2174. doi:10.1542/peds.2005-1832
14. Williams DP, Going SB, Lohman TG, et al. Body fatness and risk for elevated blood pressure, total cholesterol, and serum lipoprotein ratios in children and adolescents. *American Journal of Public Health*. 1992;82(3):358-363. doi:10.2105/ajph.82.3.358