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Childhood Obesity: Adding Metformin to Lifestyle Modification for Weight Reduction

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by

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Table of Contents

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Abstract

One of the most challenging health conditions primary care providers face is combating the ever-rising incidence of obesity, especially among children. The objective of this literature review is to determine the effects of metformin implemented in addition to lifestyle modification for the treatment of childhood obesity. Efficacy, to include change in weight, BMI, insulin resistance, and overall safety of metformin was studied. The online databases searched in this review were PubMed, Cochrane Library, Embase, and CINAHL. Literature chosen for review included randomized control trials, meta-analysis, and systematic reviews published between 2015 and 2020. Much of the studied research indicates positive effects of metformin for weight loss when added to a structured lifestyle modification plan, however, improvement in insulin resistance remains controversial. Safety analysis reveals metformin to be mostly well-tolerated among pediatric patients, with known gastrointestinal side effects being the most common adverse event. While some current research exhibits promising results for weight management, more research must be done to determine the most effective dose and treatment program length.

Childhood Obesity: Adding Metformin to Lifestyle Modification for Weight Reduction

Childhood obesity remains one of the most prevalent issues seen in the primary care setting, and it is often difficult to manage due to a myriad of factors. In the years 2015-2016, the prevalence of childhood obesity was estimated to affect over 18% of children in the United States (Hales, Carroll, Fryar, & Ogden, 2017). In pediatric patients, the definition of obesity differs when compared to obesity in adults. Body mass index (BMI) is a calculation based on height and weight and, in children, is specific to age and sex. According to the Centers for Disease Control and Prevention (2018), a BMI that is greater than the 85th percentile is considered overweight, while a BMI greater than the 95th percentile is considered obese. Dieting, healthy lifestyle modifications, and increased physical activity are regularly the mainstays of treating obesity. Pharmacotherapy options are lacking in this patient population. Failure to effectively treat obesity in children and adolescents may result in a higher likelihood of developing long-term health conditions as an adult, such as type 2 diabetes mellitus, dyslipidemia, heart disease, and hypertension (Gurnani, Birken, & Hamilton, 2015). The purpose of this study is to review the efficacy and safety of the use of metformin as a treatment option in the realm of obesity in children and adolescents.

Statement of the Problem

Childhood obesity is a rising concern among family practice providers across the country. Screening for obesity in children starting at age 6 is an important recommendation for appropriate intervention to take place in a timely manner (US Preventive Services Task Force, 2017). Traditional treatment options, to include modification of diet and exercise, are not always effective in this patient population. Orlistat is currently the only prescription approved by the United States Food and Drug Administration (US FDA) for the treatment of obesity in children,

and only in those children age 12 and older. The addition of metformin, a drug used most frequently in the treatment of type 2 diabetes mellitus, is under ongoing research for its efficacy in weight reduction and treatment of insulin resistance in obese children and adolescents. Although presently as an off-label use, if proven effective, the addition of metformin in children 10 and older would help reduce the risk of weight-related chronic health conditions, while aiding in the treatment of obesity in pediatric patients. Metformin would provide an additional treatment option for those children struggling with weight loss and the countless health implications of obesity.

Research Question

In obese children and adolescents, is adding metformin to lifestyle modification safe and beneficial in the overall reduction of weight, body mass index, and insulin resistance?

Methodology

A literature review was conducted using published research from online databases to include PubMed, Cochrane Library, Embase, and CINAHL. The review included studies published in years 2015-2020 and was limited to randomized control trials (RCTs), retrospective studies, meta-analyses, and systematic reviews. Keywords and MeSH terms were used to organize the literature into a data set focusing on treatments of childhood obesity. The data set was further defined by including only the literature analyzing the addition of metformin to lifestyle treatment plans, along with safety and efficacy of metformin in the pediatric patient population. Studies excluded were those involving adults, medications other than metformin, and children with additional diagnoses, including but not limited to diabetes, hypertension, and polycystic ovarian syndrome. Overall, nine studies met this criterion for review.

Keywords: metformin, pediatric obesity, adolescents, obesity, pharmacotherapy

Literature Review

A review of literature provides evidence that metformin therapy, in addition to lifestyle modifications, has been studied to determine efficacy, safety, and overall benefit in overweight and obese children and adolescents. Current literature shows conflicting data suggesting that metformin may or may not aid in improvement of overall glycemic control and insulin resistance, conditions often found in obese patients, ultimately leading to development of diabetes. Since the U.S. FDA has not approved obesity or weight reduction as an indication for metformin, use in the obese pediatric population is considered off-label and is not frequently utilized as a first-line therapy option.

Metformin and Weight Reduction in Obese Children

Weight reduction in obese children is a challenging issue with far fewer pharmacological options when compared to adults. Kyler et al. (2018) published a retrospective study to demonstrate outcomes of obese children prescribed metformin in the clinical setting of an endocrinology clinic. The goal of this study was to analyze effectiveness of metformin on change in weight and BMI, along with BMI z-score, over a study period of 1 year.

Methodology relied on review of electronic medical record data from a clinic specializing in endocrinology. Eligible study subjects included those 10 to 18 years old with a measured age and sex-adjusted BMI of greater than the 95th percentile at their first encounter and without previous use of metformin. Subjects were excluded if there was documentation of diagnosed diabetes mellitus, use of other antidiabetic agents, genetic or malignant conditions, or were currently taking any medications that could possibly alter weight. Record of a visit with a dietitian was identified and considered in statistical analysis, along with reported metformin side effects.

The first arm of this study included 395 subjects, with 69 prescribed metformin and the remaining 326 not prescribed metformin. The goal was to describe differences between participant baseline characteristics and between the two groups, there were significant differences (all $p < .05$) in age, baseline weight and BMI, along with BMI z-score. When comparing the groups, the metformin group consisted of older children, more often female, with higher baseline weight and BMI.

The second objective of this study involved subjects with more than one follow-up encounter, anywhere from 3 to 15 months following the initial encounter for baseline measurements. Since many were lost to follow up, this further reduced the number of total subjects assessed to 191, with 49 in the metformin group. Data was analyzed at 6 and 12-month follow-up visits, leading to additional drop in numbers due to loss of follow up. At the 12-month mark, there were 38 subjects in the metformin group and 96 in the non-metformin group. Primary measured variables included BMI and BMI z-score, and weight. The metformin group had higher baseline BMI and weight, considered statistically significant. Over the 12-month period, there was significantly less weight gain and a notable decrease in BMI noted in the metformin group.

Subgroup analyses were performed based on sex and age, specifically looking at a teen group with ages 13-17. The teen analysis reported similar findings to the main study, with significantly less gain noted in both weight and BMI in the metformin group. Analysis of female subjects included 137 girls, with 42 in the metformin group. Findings remained similar to the main study, without significant difference noted in the BMI z-score between the groups. The male group included only 54 boys, with 7 in the metformin group. There was no statistical significance reported amongst the male subgroups (Kyler et al., 2018).

Limitations to the Kyler et al. (2018) study include unknown reason for prescribing metformin, as the subjects were followed at an endocrinology clinic and may not have been prescribed metformin for weight control alone. It is also unknown if they were undergoing any other lifestyle modification. Lifestyle education was assumed to be given if there was record of a visit with a dietitian, but the dietician visits were not described in detail. Another limitation is most subjects being female tends to underrepresent males in this study. The group receiving metformin had a much lower subject count, proving to be another significant limitation of the study. Metformin dosage was not reported at all throughout the study, leaving the most effective dose of metformin in question. However, this study is valuable due to the findings of less weight gain over the course of a year of treatment with metformin compared to significantly more gain without the use of metformin (Kyler et al., 2018). This presents evidence that metformin may prove to be a beneficial adjunct to treatment plans for obese children and adolescents, but more research needs to be done to define specific dosing requirements.

A 6-month randomized controlled trial conducted at four Spanish hospitals by Pastor-Villaescusa et al. (2017) aimed at determining efficacy of metformin in reducing weight in obese children since it has already been proven to help with obesity in adult populations. The study analyzed results based on stage of puberty and sex of participants. Outcomes measured in this study include BMI, blood pressure, serum glucose and insulin, liver function tests, lipid levels, along with inflammatory and cardiovascular biomarkers.

Participants were referred from endocrinology units and randomized into two groups, a placebo and a metformin treatment group. Metformin dosage started at 50 mg with meals morning and night for 10 days, increasing to 1000 mg/day (500 mg twice daily). Participant inclusion criteria were as follows: BMI >95th percentile, 7 to 14 years of age, no previous weight

loss treatment over the last year, no previous trial involvement, and no history of or current underlying comorbidities. Each participant received lifestyle advice to include Mediterranean diet education and exercise. There were 160 children at the beginning of the trial, with 140 completing the study, 72 of those were male and 68 were female, with 67 in prepubertal stage and 73 in pubertal stage (Pastor-Villaescusa et al., 2017).

Pastor-Villaescusa et al. (2017) found a significant improvement in BMI z-score ($p = .04$) in the prepubertal group, but not the pubertal group. There was no significant difference in anthropometric measures based on sex. Insulin sensitivity was increased significantly ($p = .01$) in the prepubertal group receiving metformin compared to placebo, but not in the pubertal metformin group. Lipid levels remained stable throughout the trial amongst all groups, indicating metformin has no effect on serum lipids. Inflammatory markers, interferon-γ (IFN-γ) and total plasminogen activator inhibitor-1 (tPAI-1), were found to decrease more in the prepubertal metformin group ($p = .02$) than the placebo group ($p = .04$), though both were significantly reduced. Pastor-Villaescusa et al. also found the adiponectin-leptin ratio (ALR) increased in the prepubertal metformin group ($p = .01$), even though adiponectin and leptin levels did not show any change over the course of the study. Both pubertal groups showed no change to adiponectin, leptin, or ALR. The safety of metformin was analyzed based on adverse effects, of which the metformin group experienced more diarrhea.

One of the limitations of the study was the compliance assessment. Pill counts were done but not reported in detail, though the number of participants with good compliance was stated to be 89%. Pastor-Villaescusa et al. (2017) did not define “good compliance”, so this factor and actual compliance is unknown. It is not known whether the lifestyle interventions were adhered to during the trial. The trial only contained white Spanish children and did not go into detail on

the form of nutritional advice each participant received. Metformin dosage was uniform across the study, without regard to weight, so the pubertal stage group received a lower dose per kilogram of body weight than the prepubertal stage group, possibly contributing to the lack of results found amongst the pubertal group.

Overall, this study provides analysis of the effects of metformin regarding BMI z-score in those children who are overweight or obese, while taking pubertal status into account. Pubertal stage may need to be a consideration in use of metformin, along with weight-based dose calculations to achieve maximum efficacy. Pastor-Villaescusa et al. (2017) provides evidence that pubertal stage is an important variable to consider when deciding to add metformin to treatment plans for obese children.

A retrospective study conducted by Scinta and Morley (2015) analyzed medical records from children who participated in the BOUNCE program to provide evaluation of initial results. BOUNCE is a program designed for obese and overweight children. The program includes many components such as the use of a biguanide (metformin) and behavioral modifications, optimizing the metabolism via specific meal plans, a unique approach to ensure family unity and involvement, food logs, daily step counting with a pedometer, and lastly, dieting based on reduction and/or elimination of foods high in calories and carbohydrates. In addition, the program also encourages regular exercise. The program included biweekly visits with the subjects and occasionally their family members, along with monthly dietitian visits (Scinta & Morley, 2015).

Scinta and Morley (2015) analyzed data that was gathered from the electronic medical records of the first 50 participants in the BOUNCE program. The calculated outcomes of this chart review were weight lost per month (WLM) and total weight lost (WL), decrease in BMI

(BMIL), and total percent BMI lost throughout the program (PBMIL). There were 53 participant records initially analyzed, but three were excluded due to lack of necessary data. Subject data was placed into groups based on those that dropped out at any stage of the study, those currently in the program, and those that completed the program (Scinta & Morley, 2015).

The participant sample from the BOUNCE program was mostly female (n = 35), with ages ranging from 9 to 19 years. Participation in the program was, on average, 7.53 months, resulting in average weight loss of 14.75 pounds. Mean BMI at the beginning of the program was 33.85 kg/m^2, with end results of a mean of 30.08 kg/m^2. Analysis of compliance showed exercise, five meals/day plan, and elimination diet had the greatest adherence, which Scinta and Morley (2015) reported as 100%, 94%, and 90%, respectively. Step counting and food diaries were adhered to 52% of the time.

Results showed that all three groups lost weight. There were 26 participants that dropped out of the program, but still achieved mean weight loss of 9.74 pounds and a decrease in BMI by 1.93 kg/m^2. The current participant group (n = 18) showed a mean weight loss of 18.79 pounds, with a 3.56 kg/m^2 drop in BMI. Subjects that completed the program (n = 6) exhibited mean weight loss of 25.83 pounds and BMI decrease of 5.13 kg/m^2. BMI loss between these groups was statistically significant. Results varied based on age and time in the program, but older participants lost more weight overall (Scinta & Morley, 2015).

Limitations of the study published by Scinta & Morley (2015) include little analysis of each component of the program model, without clear definition of which subjects, to include age and gender, had the most weight and/or BMI loss, as well as whether they were compliant with all program measures. With a high drop-out rate due to reported lack of familial support, the

small sample size of subjects currently in or who have completed the program reduces the power of the study.

This study provides useful information by exhibiting significant weight loss and BMI reduction in those participants that completed the study, even though the participants that dropped out also showed weight loss and improvement in BMI (Scinta & Morley, 2015). This gives evidence that including metformin in a comprehensive weight loss treatment program may provide more benefit to obese and overweight children than lifestyle changes alone. This study also provides insight on the correlation between familial involvement and adherence to treatment parameters.

To determine the efficacy of metformin for weight management, Warnakulasuriva et al. (2018) conducted a 12-month triple-blind RCT on children with obesity in Sri Lanka. This study contained two arms, with both containing a structured diet and exercise plan. In addition, one arm received metformin while the other arm received a placebo.

Methods included screening programs through schools in the region of the study, along with a subsequent invitation to those eligible for participation. To be eligible, subjects were required to be obese and aged 8-16 years. Participants were placed into groups by age, 8-10 and 11-16 years. Following baseline measurements, each age group was randomly placed into the study arms. In the metformin group, those 8-10 years old started at a dose of 250 mg per day for one week, then 250 mg two times per day for another week, and lastly increased to 500 mg twice per day for the remainder of the study. The older children, 11 to 16-year-olds, were started on 500 mg two times per day for one week, followed by an increase to 1000 mg twice a day. To reduce gastrointestinal effects and possible hypoglycemia, metformin was given with meals. The diet and exercise programs in each study arm included education from a nutritionist with portion

guidelines given to the subjects and their parents, along with a home schedule of 20-30 minutes of physical exercise each day provided by a physical trainer. Home workout plans would change monthly. Weekly 1-hour training sessions were carried out for both groups, where the participants would also bring their exercise journal for compliance monitoring and assessment. Follow-up visits occurred 2 weeks from the start of therapy and monthly thereafter, where body measurements were done, with phone calls every week for the first 4 weeks and then every 2 weeks following. These visits monitored compliance and addressed concerns. Fasting blood tests were drawn at baseline, 6 months, and 12 months (Warnakulasuriva et al., 2018).

A total of 339 eligible subjects registered for the trial and were randomized into groups. Of the 339 subjects, 189 withdrew from the trial at various times resulting in a final analysis of only those that participated in the trial until completion (n = 150), 68 were in the metformin group (Warnakulasuriva et al., 2018).

The primary outcomes measured were BMI/Age and percentage of fat mass (%FM/Age). reported a significant reduction in BMI/Age at both 6 and 12 months in the metformin group when compared to placebo. A greater reduction in %FM/Age at 6 months was reported to be significant in the metformin group ($p = .04$), with sustained reduction in both groups at 12 months without significant difference ($p = .131$).

Warnakulasuriva et al. (2018) reported the secondary measures to be weight, waist circumference (WC), weight-to-height ratio (WHtR), blood pressure (BP), fasting blood glucose (FBG), and serum insulin obtained via HOMA-IR measurement. At 6 months, there was significant decrease in weight in those taking metformin, compared to an increase in weight for those in the placebo group. Weight gain was reported in both groups by 12 months and was assumed that overall growth of the child contributed to the gain, though this gain was

significantly less in the subjects receiving metformin ($p = .001$). Reduction in WC and WHtR were significantly greater in the metformin group at both 6-month and 12-month intervals. WC/Age exhibited increased reduction, though not significant, at 6 months in the metformin group compared to placebo, with significant reduction noted at 12 months ($p = .018$). There was a larger decrease in systolic BP found to be significant in the metformin group at 6 months and this reduction continued at 12 months. Diastolic BP did not have a significant decrease between either of the groups. Levels of FBG, serum insulin, and HOMA-IR showed no significant improvements in either group (Warnakulasuriva et al., 2018).

Metabolic measurements included cholesterol levels, liver function tests (ALT and AST), and highly sensitive C-reactive protein (hs-CRP). Total cholesterol and low-density lipoprotein levels were significantly reduced at 6 months in those taking metformin, but this was not found to be true at 12 months. Triglyceride levels were found to be significantly reduced in the metformin group at 12 months. There was no improvement deemed significant in high-density lipoprotein for either group. The metformin group exhibited a significant reduction in hs-CRP at 6 months only. No significant reductions in ALT and AST were found in either group (Warnakulasuriva et al., 2018).

A subsequent analysis was performed to account for age, gender, and stage of puberty. The reported metformin effects on BMI, percent fat mass, and WC were only recorded in the older age group (11 to 16-year-olds), providing evidence that age influences the outcomes of treatment. Analysis based on gender revealed significance in metformin efficacy in females compared to males when assessing WC, WHtR, and systolic BP. In the metformin group, pubertal subjects were found to have greater changes in percent fat mass and WC (Warnakulasuriva et al., 2018).

Limitations of this study include the high rate of participant dropout without explanation of reasoning. As noted by Warnakulasuriva et al. (2018), the sample sizes for the subgroup analyses were not adequate for each group, decreasing the overall power of this portion of the study. The measurement of physical activity and exercise compliance was not reported in detail, but all participants were assumed to be adherent to the guidelines set forth.

Even though the dropout rate was high, this study included the largest sample size throughout the whole 12-month trial when compared to previously published studies. The results of this study provide evidence that there may be significant benefit in adding metformin into the lifestyle modification treatment plan for weight loss in obese children. This study also shows that age and pubertal status are important variables when considering off-label metformin treatment in obese children.

Effects of Metformin on Insulin Resistance in Obese Children

Insulin resistance is frequently found among obese children and carries the potential to lead to development of type 2 diabetes mellitus. Reducing insulin resistance in obese children would have a positive effect on improvement in overall health. Lentferink et al. (2018) published the results of an open-label extension study immediately following a randomized controlled trial which studied the effects of metformin in obese and insulin resistant adolescents. Each study had a duration of 18 months. The goal of the extension study was to provide outcomes of long-term metformin treatment with regards to efficacy and overall safety of the drug.

Participants in the Lentferink et al. (2018) extension study were blinded to the treatment (metformin or placebo) they were taking during the 18-month RCT. At the conclusion of the trial, participants were offered metformin if they were still considered obese and insulin resistant, regardless of which treatment group they were previously in. Those who did not meet criteria or

rejected metformin treatment were not given metformin during the entirety of the 18-month extension study but were still included in analysis. The four arms of this study were based on which treatments the participants received and are listed as follows: metformin in the RCT and extension study (MM), metformin in the RCT with placebo in the extension study (MP), placebo in the RCT and extension study (PP), and placebo in the RCT with metformin in the extension study (PM) . Due to failure of follow-up, 31 of the 42 RCT participants completed the extension study, with 11 of those receiving metformin. Outcomes measured were change in BMI, insulin resistance using the Homeostasis Model Assessment for Insulin Resistance (HOMA-IR), body fat percentage, quality of life, physical fitness, and glycated hemoglobin. Safety was evaluated using hepatic and renal function tests, along with vitamin B12 levels, while tolerability of metformin was evaluated based on reported side effects and any required decrease in dosage. Complications to metabolic and cardiovascular systems were also analyzed (Lentferink et al., 2018).

As reported by Lentferink et al. (2018), the PM group showed an initial decrease in BMI for the first 6 months of the extension study, however BMI increased thereafter. In the MM group there was a BMI increase noted throughout the entire study. The MP group showed a stable BMI at the 6-month assessment, with an increase in BMI at the end of the study. The PP group reported an increase in BMI over the initial 6 months, but this stabilized by the end of the study. There was a significant increase in HOMA-IR in the MM group. All other groups (MP, PM, PP) showed an initial increase in HOMA-IR with a subsequent decrease by the end (Lentferink et al., 2018). These results indicate there may not be positive long-term effects with a prolonged metformin treatment regimen. Lentferink et al. acknowledged there were no serious

side effects reported and metformin was overall tolerated well by the participants, with only 2 subjects dropping out due to gastrointestinal side effects.

Limitations to this open-label extension study are numerous. The overall sample size is small, with only 11 subjects treated with metformin by the end of the extension study. There were no compliance pill counts done in the extension study even though this had been assessed in the initial RCT. Compliance is a major factor when determining efficacy of a therapy program, so lack of compliance monitoring reduces the power of this study. According to Lentferink et al. (2018) there were reports of some participants not adhering to daily metformin, which could indicate ineffective treatment. It is noted that the consistent weight gain noticed in some subjects could be the result of inadequate dosing, as most of these subjects weighed greater than 100 kg. It is unclear whether all participants who received metformin were on the target of 2000 mg/day, possibly leading to inadequate treatment if target dosage was not achieved. The planned physical fitness and quality of life analyses were not done due to lack of participant cooperation. Pubertal stage was not adjusted for in the measurements at the end of the extension study, as most of the participants were post-pubertal by that point.

This study provides some evidence that extended obesity treatment plans for greater than 18 months with metformin may not provide heightened benefit compared to that of shorter duration. There were plenty of limitations to this study, warranting further research into long-term follow-up for metformin treatment and the effects on insulin resistance.

Another randomized controlled trial was published by Li, Li, and Kong (2019) to evaluate the overall efficacy of adding metformin to lifestyle modification for treatment of obesity and hyperinsulinemia in children and adolescents. This 6-month study took place at Army Eighty-three Group Army Hospital, where 84 children suffering obesity and

hyperinsulinemia were admitted from January 2017 to June 2017. These children were randomized into control and treatment groups. The control group was given healthy recipes, caloric intake goals, aid in changing their eating habits and greater than half hour of exercise each day. The treatment group was given the same parameters with the addition of metformin 30 minutes before meals, three times per day. Dose varied based on age, 250 mg/dose (750 mg/day) for those under 8 years old and 500 mg/dose (1500 mg/day) for those 8 and older (Li, Li, & Kong, 2019).

Outcomes measured by Li, Li and Kong (2019) were change in BMI, waist circumference (WC), waist-to-hip ratio (WHR), and waist-to-height ratio (WHtR). These variables were measured at the beginning and end of the trial. Fasting insulin (FINS), insulin one hour after glucose load (INS-1h), and insulin two hours after glucose load (INS-2h) were measured at baseline and at the end of the study, as well. Serum glucose was measured the same as insulin with measurements taken fasting (FPG), one hour after glucose load (PG-1h) and two hours after glucose load (PG-2h). This study also investigated HOMA-IR, total cholesterol (TC), and triglyceride (TG) levels (Li, Li, & Kong, 2019).

The results Li, Li, and Kong (2019) found show a significant change in BMI in both groups when compared to baseline, though there was not a statistically significant difference between the control and treatment groups. Significant decreases in WC, WHR, and WHtR levels were noted in both groups compared to baseline, with a greater significance in those taking metformin (all $p < .05$). The study also found significantly lower FINS, INS-1h and INS-2h levels (all $p < .05$) in those receiving metformin compared to diet and exercise alone. PG-1h and PG-2h levels decreased significantly from baseline in the metformin group and a decrease in PG-2h was found in the control group, but the metformin group showed significantly lower ($p < .05$)

glucose levels than the control group. HOMA-IR improved significantly in the metformin group, along with TC and TG levels (Li, Li, & Kong, 2019).

Limitations of this study include a smaller sample size contributing to possible biased outcomes. Li, Li, and Kong (2019) did not analyze safety indices or adverse events that occurred during the treatment with metformin, so tolerability and safety of the medication in addition to lifestyle modification is not documented.

Li, Li and Kong's (2019) study presents helpful evidence based on the positive results metformin has on BMI, insulin resistance and blood glucose levels. All these factors play a large role in combating childhood obesity and controlling them may help prevent complications. This trial provides evidence that adding metformin to a 6-month lifestyle modification treatment plan may be beneficial to overall health, but future studies with larger sample sizes are warranted.

Sun et al. (2019) compiled a meta-analysis reviewing the efficacy of metformin on improvement in HOMA-IR in obese children and adolescents not suffering from other comorbidities. The goal of this systematic review was to assess the ability of metformin to improve insulin resistance, as its efficacy in BMI reduction has been well studied. There were 11 RCTs eligible for inclusion in this meta-analysis with 865 total participants. Age of all subjects ranged from 4-18 years, with dose of metformin between 1000 mg and 2000 mg per day. Trial duration of the randomized controlled trials varied from 2-18 months (Sun et al., 2019).

One of the outcomes measured by Sun et al. (2019) included change in insulin resistance utilizing HOMA-IR, serum glucose, lipid panel, and fasting insulin. Of the 11 RCTs, 9 studies described a change in HOMA-IR, but Sun et al. reported no significant decrease between metformin and placebo. In other words, this meta-analysis found no significant improvement in insulin resistance by adding metformin to lifestyle changes. In the six studies analyzing fasting

serum glucose, a significant difference in improvement was noted in metformin groups for treatment periods of fewer than 6 months, but this difference was not significant in those treated for 6 months or longer. Fasting insulin was measured in seven of the trials, with overall results indicating the addition of metformin to lifestyle changes can lower fasting insulin, and the difference is significant when compared to placebo. No improvement was found in the eight studies measuring high density lipoprotein levels, but there was significant difference in lowering low density lipoprotein levels in metformin groups, as reported in six studies (Sun et al., 2019).

Sun et al. (2019) found adverse effects of metformin and placebo treatments were reported in 10 studies, where six studies analyzed which adverse effects occurred and to whom they affected. Frequently reported were gastrointestinal effects including nausea, diarrhea, vomiting, and abdominal pain, along with headache and dizziness. Adverse events were often remedied by a reduction in dosage or termination of the medication (Sun et al., 2019).

This meta-analysis by Sun et al. (2019) is not without limitations. The analysis only focuses on published literature and there were only 11 RCTs included in this analysis with 3 having relatively small sample sizes (< 35 subjects). In depth detailed results of each RCT were not included, but rather just overall results. Each study included in this review had a different length of treatment and included varying doses of metformin. Treatment adherence during these studies is also not addressed, so it is unknown whether the results are truly accurate.

This review by Sun et al. (2019) provides beneficial analysis of multiple studies and their results regarding insulin resistance improvement with metformin therapy. While other studies have shown that HOMA-IR does indeed improve with metformin and lifestyle modification, this

review found contradicting results, indicating a need for further research and more robust controlled trials.

An 18-month randomized controlled trial conducted by van der Aa et al. (2016) was designed to establish the impact of metformin usage with scheduled physical activity in obese adolescents with insulin resistance. The main goal was to describe efficacy of long-term metformin treatment pertaining to insulin resistance and BMI change, along with safety of the medication, glycated hemoglobin (HbA1c), fitness levels, and overall quality of life.

Subjects were randomized into either metformin or placebo allocations, while staff and subjects were blinded during the entire 18-month study. Recruitment took place at participating pediatric outpatient facilities in the Netherlands (van der Aa et al., 2016). To be included in the study, participants had to be Caucasian adolescents between 10 and 16 years old with specific BMI and HOMA-IR requirements. Participants were excluded if they were pregnant, had any endocrine disorders, renal or hepatic impairment, or any other syndromes. A total of 62 subjects were randomized into groups but drop-outs and failure to follow up reduced the final participant number to 23 in the metformin group and 19 in the placebo group (total n = 42). The metformin group received immediate-release 500 mg tablets in a titrated fashion, to a maximum dose of 2000 mg per day by week 4 of the study. Pill counts were done every 3 months to measure subject compliance. Training classes were offered by a physical therapist twice a week. Primary outcome measures to include change in BMI, HOMA-IR, and glucose, were performed at 3-month interval follow-up visits for the duration of the 18-month study. Physical fitness with various tests and a quality of life questionnaire were conducted at baseline and at completion of the study. Safety was a secondary outcome measured every 3 months by assessing renal and hepatic function, vitamin B12 levels, and reported adverse side effects. Tolerability was

measured by maximum dosage achieved and adverse side effects. Subjects were instructed to complete a diary of their intake to calculate their individual caloric needs and this diary was to be assessed at baseline, half-way through, and at the end of the study (van der Aa et al., 2016).

Primary outcome results reported by van der Aa et al. (2016) show a significantly larger increase in BMI in the placebo group compared to those treated with metformin. In the metformin group, there was a decrease in BMI for the first 6-9 months, with BMI returning to near baseline thereafter. There was not an initial BMI decrease noted in the placebo group. No significant difference was reported for change in HOMA-IR between groups, nor from baseline to end of study. Both groups indicate an increase in HbA1c, but this was significantly higher in those receiving placebo, and no participant had a value above normal limit. Change in body fat percentage was not significant, but the metformin group resulted in significant decrease of overall fat mass and increased fat-free mass (van der Aa et al., 2016).

Safety outcome results demonstrate no severe side effects or impairment of renal or hepatic function. Adverse side effects reported were nausea and diarrhea, more so in the metformin group, although only the increased nausea was statistically significant. Maximum dose of metformin was tolerated by all but four participants, who subsequently required reduction to either 1000 mg or 1500 mg daily. Vitamin B12 levels were below the study-specific safety threshold in three subjects at conclusion of the study, but this level was still within normal range. Quality of life questionnaire administered at the end of the study revealed no change from baseline (van der Aa et al., 2016).

One limitation of the study as reported by van der Aa et al. (2016) is the much smaller sample size than was calculated to provide effective results. Another limitation is treatment compliance, as conducted pill counts could not be performed on every subject, and those that did

return the pill packages often contained more medication than would be considered 100% compliance. Physical training sessions were poorly attended, not allowing for full analysis of physical fitness levels. Diaries with individual dietary intake were not completed to the necessary extent, so caloric need was not able to be assessed and calculated.

This study offers some valuable information. While metformin proves to improve BMI indices in obese children, improvement in insulin resistance remains controversial. Due to the small sample size and questionable compliance, further research is required to fully evaluate long-term effects of metformin on insulin resistance in obese children and adolescents.

Safety of Metformin in Pediatric Patients

Overall safety must be considered when prescribing any medication, especially when the patient at hand is a child. Marques et al. (2016) organized a retrospective study of medical records of pediatric patients of whom were overweight or obese without diagnosis of diabetes and were receiving metformin. Record review compared weight loss, change in insulin resistance, and safety indices of those receiving treatment with metformin to modification to lifestyle with follow-up data documented at 1 and 2 years from the start of treatment.

The records of 78 patients were used for this retrospective study (Marques et al., 2016). Two groups, both including lifestyle modifications with one group adding metformin, were identified and both included 39 participants. Data was reviewed at baseline, 12 months, and 24 months, with completion of follow-up documentation in 78, 74, and 37 patients, respectively. Of the metformin group, 16 patients had documentation for the whole study, including the 24-month follow-up visit. The main outcome Marques et al. (2016) measured was change in BMI, with secondary measurements for change in insulin resistance using HOMA-IR and lipid levels. Metformin dosage varied among patients, with 12 receiving 1000 mg daily, 4 receiving 500 mg

daily, 7 at 2000 mg daily, and the others with undisclosed intermediate daily dosage (Marques et al., 2016).

Results show baseline weight and BMI, along with HOMA-IR and triglyceride level was significantly higher in those treated with metformin compared to only lifestyle modification. Marques et al. (2016) found a gradual decrease in BMI in both groups at 12 months, and no significant change noted in the control group at 24 months. Both groups showed significant decrease in BMI when compared to baseline, but there was no significance when the groups were directly compared to each other.

Marques et al. (2016) also analyze the safety of metformin. Of the metformin group, five subjects reported medication side effects with four requiring a decrease in dosage due to these side effects, including nausea and vomiting. Gastrointestinal symptoms are commonly known side effects of metformin. None of the members of the metformin group had to completely discontinue the medication, proving this medication to be relatively safe. The documented side effects analyzed in this study were somewhat inferior to previously reported rates of other studies according to Marques et al.

The lifestyle intervention group is not described in any detail, demonstrating a limitation of this study. Being this is a retrospective study, Marques et al. (2016) were limited to only using data that is documented, providing possible inconsistencies with actual clinical outcomes if there is a lack of documentation. The variable metformin dosage is another limitation to the study, as results are not defined based on dosage, but as a whole group. The overall sample size is small, and the rate of patient dropout was high at 24 months.

This study is beneficial for this project due to the positive results regarding safety of metformin. The known gastrointestinal side effects of this drug are the most reported and were

able to be remedied with dose adjustment. This provides evidence that metformin may be safely used in the pediatric patient population, but more research needs to be done to determine the most effective and safest dose.

Safety of metformin, in reference to side effects only, was a small objective in the previously discussed retrospective study published by Kyler et al. (2018). Adverse symptoms were reported in 37% of the subjects that received metformin, with gastrointestinal symptoms, to include abdominal pain, nausea, vomiting, and diarrhea, being the most pronounced (Kyler et al., 2018). It is well known that gastrointestinal side effects are associated with the use of metformin in diabetic patients, so the reported side effects in this study are no surprise. Kyler et al. found no subjects reported to experience lactic acidosis, an extremely rare side effect of metformin. These findings provide useful information for this review, as there were no serious adverse events associated with metformin use in children, which helps to identify this medication as relatively safe.

The randomized controlled trial performed by Pastor-Villaescusa et al. (2017) aimed to address pubertal status as a factor when considering the overall efficacy and safety of metformin used for weight loss in obese children and adolescents. The main outcomes of the study are reported and analyzed above, while safety is discussed here. The study reported that metformin was tolerated well without any subjects requiring discontinuation of the drug due to side effects (Pastor-Villaescusa et al., 2017). Pastor-Villaescusa et al. also reported both placebo and metformin groups experienced diarrhea, however, there was slightly more in the metformin group. The rare, but serious, development of lactic acidosis was not reported among these subjects. This study is valuable to this review as it found metformin to be safe and tolerable, without any serious or life-threatening complications.

Sun et al. (2019) compiled a meta-analysis and systematic review of 11 randomized controlled trials to determine how well metformin treats insulin resistance in overweight and obese children, along with the relative safety of metformin based on adverse events. Of the studies analyzed, all but one reported adverse events and safety as part of the measured outcomes of the study. As found by many other studies, gastrointestinal side effects such as nausea, vomiting, and diarrhea, along with headache and dizziness, were found to be the most frequently reported adverse event in those taking metformin (Sun et al., 2019). It was found that most of the side effects were reduced or resolved with dose adjustment. This study reveals that monitoring for side effects and adjusting metformin dose enhances tolerability and contributes to the overall safety of this drug.

Long-term metformin effects in obese children were studied and published by van der Aa et al. (2016). The primary outcomes of this study have been discussed previously. The secondary outcomes of this study include safety and tolerability of metformin (van der Aa et al., 2016). The study reported no serious adverse side effects or events between the metformin or placebo group. van der Aa et al. also found no decline in function or injury to the renal or hepatic systems, as measured via testing of glomerular filtration rate (GFR) and liver function tests, to include alanine aminotransferase (ALT). These tests were obtained at baseline and every three months throughout the 18-month study. In addition, van der Aa et al. monitored vitamin B12 levels and reported that three subjects fell below the study safety threshold, though this level was not below normal reported value. Tolerability was measured by ability to achieve maximum metformin dosage of 2000 mg/day. The two subjects that discontinued participation in the study were lost to follow-up due to severe nausea and abdominal pain (van der Aa et al., 2016). There were four subjects that did not tolerate the maximum dosage, but dose adjustment was successful in

achieving tolerability. As expected, gastrointestinal side effects were reported among both placebo and metformin groups, with nausea being more significant in those taking metformin. This study indicates that metformin is relatively safe and tolerable. Gastrointestinal side effects are well known and adjusting the metformin dose may be necessary in some patients.

Discussion

While there are numerous studies indicating the importance of lifestyle modification for the treatment of childhood obesity, there is not one single proven diet and exercise regimen that will work for all. Pharmacotherapy is utilized more in the adult patient population, as there are many more medications approved for weight loss in the adult. For adults, when diet and exercise alone are unable to achieve weight loss goals, medications are often the next step of the algorithm. Lifestyle modification has been the mainstay of treatment for children, but as the obesity rate continues to climb it has proven that additional treatment options need to be validated. Finding an adjunctive treatment to lifestyle changes is crucial in the fight of childhood obesity. While currently an off-label use, metformin has been studied and analyzed for its use in the realm of childhood obesity, but further research must be done to determine the most effective dose and treatment length.

Does Metformin Help with Overall Weight Loss in Obese Children?

Weight reduction and overall improvement in BMI among obese children is key in reducing the risk of obesity-related chronic health issues such as diabetes, hypertension, dyslipidemias, and heart disease. The study published by Kyler et al. (2018) found significantly less weight gain over a period of 12 months with an overall decrease in BMI reported among the children and adolescents treated with metformin. While less weight gain cannot be directly interpreted as weight loss, these results reveal the use of metformin as an adjunct to diet and

exercise may be beneficial to help lower the overall weight gain often observed in overweight and obese children. To add, Warnakulasuriya et al. (2018) also found weight gain to be significantly less over a 12-month period in those treated with metformin, with the initial 6 months resulting in overall weight loss. The subsequent weight gain is likely associated with the fact that the children in these studies are indeed children and are not finished growing.

Through published studies, puberty has proven to be a large factor in the effectiveness found in metformin. Pastor-Villaescusa et al. (2017) found that a dose of 500 mg twice a day resulted in significant improvement in BMI z-score in prepubertal obese children but not the children in the pubertal group. Due to the metformin dosage being the same among both groups, the prepubertal children received a higher weight-based dose, which may have added to the overall efficacy of the medication. This could also explain the lack of results among the pubertal group, as they received a lesser dose based on their weight (Pastor-Villaescusa et al., 2017). The differing results in this study indicate that pubertal status is an important consideration in use of metformin for obese children and adolescents. Weight-based dosing may be another factor to consider when utilizing metformin for weight loss in this population.

The results published by Scinta and Morley (2015) revealed positive initial results on the use of metformin in a complex treatment program for obese children. Among the six subjects that completed the full program, mean weight reduction was significant at 25.83 pounds (Scinta & Morley, 2015). Despite the high drop-out rate in this program, the significant weight and BMI loss noted in all groups suggests that including metformin in a comprehensive weight loss treatment program may provide more benefit to obese and overweight children than simple lifestyle changes alone, even if the use of metformin is not long-term. This study also drives

home the idea that a comprehensive program that can be individualized to each patient can provide more positive outcomes.

Overall, pubertal status, gender, age, and baseline weight are all factors that must be considered when initiating metformin therapy for weight management in obese children. The varying doses of metformin in each study complements the notion that further research must be obtained to determine overall efficacy.

Does Metformin Help Lower Insulin Resistance in Obese Children?

Insulin resistance is commonly found among obese individuals and is one of the leading causes of the development of diabetes in obese children. Increasing insulin sensitivity while treating obesity would be highly beneficial and possibly reduce the incidence of type 2 diabetes mellitus among children. The results published by Lentferink et al. (2018) indicated that 36 months of metformin treatment does not decrease insulin resistance, as HOMA-IR was actually found to increase. This study shows that while metformin may initially improve insulin resistance, long-term treatment of greater than 18 months may not provide any benefit or improvement in insulin resistance.

Li, Li, and Kong (2019) found opposing results during a 6-month RCT. HOMA-IR was found to decrease significantly in those taking metformin, along with insulin levels and plasma glucose levels. These results exemplify the effects of metformin on plasma glucose and insulin levels, with a positive outcome in insulin resistance, a factor that plays a large role in childhood obesity.

Similarly, the randomized controlled trial conducted by Pastor-Villaescusa et al. (2017) found metformin treatment to result in a significant increase in insulin sensitivity ($p = .01$) among the subjects in the prepubertal group receiving metformin compared to placebo. However,

this was not reported in the pubertal metformin group. It is easy to conclude that pubertal status remains a large variable in the effectiveness of metformin.

In the meta-analysis published by Sun et al., (2019), the use of metformin for improving HOMA-IR in obese children and adolescents was analyzed. Once again, there are conflicting results showing no significant decrease in insulin resistance between metformin and placebo. In addition, van der Aa et al, (2016) also reported no significant change in HOMA-IR between metformin and placebo treatment groups. Improvement in insulin resistance among obese children receiving metformin remains highly controversial, warranting further research with much larger sample sizes.

In addition, the 12-month triple-blind RCT conducted by Warnakulasuriva et al. (2018) in Sri Lanka revealed that neither the metformin or placebo group had any significant improvement in serum insulin or HOMA-IR, along with fasting blood glucose levels. This further indicates that much research must be done to determine the efficacy of metformin regarding insulin resistance among obese children and adolescents.

Is Metformin Safe for Treatment in Obese Children?

Prior to starting any medication regimen, safety of the treatment must be considered and deemed probable to produce an overall benefit that outweighs the risk. The retrospective study published by Marques et al. (2016) found nausea and vomiting to be the most reported side effects in the study. As gastrointestinal side effects are well-known to be associated with metformin, this comes as no surprise. There were no members of the metformin group that required discontinuation of metformin due to side effects, providing evidence that metformin is relatively safe and adverse effects can often be remedied with dose adjustment (Marques et al., 2016).

Another study produced results indicating metformin is relatively safe in pediatric patient populations. van der Aa et al. (2016) found no severe side effects, along with no impairment of renal or hepatic function among participants. The most commonly reported adverse side effects were nausea and diarrhea, with more diarrhea reported in those taking metformin. Again, gastrointestinal side effects are well known side effects of the medication and were not significant enough to warrant discontinuation of the drug. Those who did have symptoms at maximum dose (2000 mg) were given a reduced dosage to enhance tolerability. Overall, these results conclude that metformin is reasonably safe among children with side effects being easily reduced by simple dose adjustments.

In the 18-month open label extension study published by Lentferink et al. (2018), long-term safety of metformin was another component of the analysis. This study was without any report of serious side effects, while gastrointestinal symptoms resulted in the drop-out of 2 participants. Along with efficacy of metformin, Pastor-Villaescusa et al. (2017) also analyzed the safety of the drug based on adverse effects. In this RCT both groups experienced diarrhea, but this was more notable in the metformin group. Gastrointestinal side effects were also of the most reported adverse effects in the study published by Kyler et al. (2018). To conclude, throughout all studies that reported on safety, most of them analyzed this by way of reported side effects. It is well known that metformin may cause gastrointestinal issues, and these were by far the most reported side effects, deeming the medication relatively safe among this population without great risk of significant adverse events.

Conclusion

The findings of this review suggest that metformin may be a useful medication to provide added weight management and control in obese children. There is no single effective dose or

length of treatment found to date and age, gender, weight, and pubertal status must be taken into consideration. It remains to be proven if metformin improves insulin resistance factors as many studies provide conflicting results, so more research must be done to determine this. Overall, metformin appears to be a safe medication to use in pediatric patients, with gastrointestinal side effects being the most reported adverse event. Tolerability of metformin can often be remedied with dose adjustment and out of all the studies analyzed, very few subjects required termination of study participation based on safety and side effects of metformin.

Applicability to Clinical Practice

This literature review applies to every day clinical practice based on the increasing numbers of overweight and obese pediatric patients seen in many primary care clinics. Treatment in this patient population can be challenging as there is no perfect protocol or recommendation proven completely effective for treating and overcoming childhood obesity. The information provided will allow healthcare providers to make an informed and evidence-based decision regarding the utilization of metformin as an adjunctive therapy option when lifestyle modification treatment programs alone have failed to provide sufficient benefit to the complex problem that is childhood obesity. The literature suggests that age, gender, weight and pubertal status all play an important role in the decision to treat with metformin, along with determining the appropriate dose and treatment length.

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