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Childhood Obesity: Adding Metformin to Lifestyle Modification for Weight Reduction

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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.

Introduction

Between 2015-2016, the prevalence of childhood obesity was estimated to effect >18% of children in the United States (Hales, Carroll, Fryar, & Ogden, 2017). BMI is calculated 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 >85th percentile is considered overweight, while a BMI >95th percentile is considered obese. Failure to effectively treat obesity in children may result in a higher likelihood of developing long-term health conditions as an adult.

Statement of the Problem

Traditional treatment options, to include modification of diet and exercise, are not always effective for obese children. Pharmacotherapy options are lacking in this population. The addition of metformin is under ongoing research for its efficacy in weight reduction and treatment of insulin resistance in this population. If proven effective, the addition of metformin in children 10 and older would help reduce the risk of weight-related chronic health conditions while treating 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?

Literature Review

Metformin and Weight Reduction

- Kyler et al. (2018) published a 12-month retrospective study of obese children in an endocrinology clinic and found significantly less weight gain and a notable decrease in BMI in the metformin group.
- Pastor-Villaescusa et al. (2017) performed a 6-month RCT in four Spanish hospitals. Maximum metformin dosage was1000 mg/day. Results were based on pubertal status. They found a significant improvement in BMI z-score (p = .04) in the prepubertal group receiving metformin, but not the pubertal group.
- Scinta and Morley (2015) analyzed data from initial results of the first 50 participants of the BOUNCE program, a comprehensive plan for overweight children. Mean weight loss was 25.83 pounds and BMI decreased by 5.13 kg/m^2 in the children who completed the program (n = 6), though those that dropped out or had not yet completed the study also showed weight and BMI loss.
- Warnakulasuriva et al. (2018) performed a 12-month RCT in Sri Lanka and found significant reduction in BMI among those who received metformin, along with greater reduction in percentage of fat mass compared to placebo. These results were notable in those subjects of pubertal status.

Effects of Metformin on Insulin Resistance

- Lentferink et al. (2018) studied subjects enrolled in an 18-month extension study following an 18-month RCT. Results indicate those who took metformin for both studies actually had an increase in insulin resistance, but those who took metformin for only one of the studies had a decrease in HOMA-IR.
- Li, Li, and Kong (2019) performed a 6-month RCT studying metformin effects on obese children with hyperinsulinemia. Results indicate a significant improvement in HOMA-IR among the children taking metformin.
- Sun et al. (2019) compiled a meta-analysis studying 11 RCTs involving obese children. Trial duration and metformin dosage varied. Nine studies found a change in HOMA-IR, but there was no significant decrease when comparing metformin to placebo.
- van der Aa et al. (2016) found no significant change in HOMA-IR in subjects taking metformin or placebo during an 18-month RCT.

Safety of Metformin

- Marques et al. (2016) performed a retrospective study to analyze long-term effects of metformin in obese children. Findings indicate metformin, overall, is safe and tolerated well in this population. GI side effects are well known and expected, and often remedied with dose adjustment.
- Kyler et al. (2018) found GI symptoms to be the most common. There were no serious adverse events, to include lactic acidosis.
- Pastor-Villaescusa et al. (2017) did not report any subjects dropping out of the study due to adverse events. Both placebo and metformin groups reported GI symptoms, more so in the metformin group.

Discussion

Does Metformin Help with Overall Weight Loss in Obese Children?

- Adding metformin to diet and exercise may help lower the overall weight gain of obese children as they age, as the results published by Kyler et al. (2018) found significantly less weight gain over the course of 1 year.
- Since Warnakulasuriva et al. (2018) also noted less weight gain over a 12-month period and initial weight loss during the first 6 months, it is apparent that when studying children, the normal weight gain as the child ages must be accounted for. Less weight gain may still benefit the overall health of the child.
- Puberty is a large factor in metformin effectiveness, as shown by multiple studies. Pastor-Villaescusa et al. (2017) showcased that prepubertal children had better results with metformin compared to pubertal. Weight of pubertal children is often higher than prepubertal, so dose may need to be more weight-based for children going through pubertal changes.
- Complex treatment programs that include metformin, such as the BOUNCE program, exhibit great results with significant weight and BMI loss (Scinta & Morley, 2015). Programs should be individualized to meet each child's needs.

Does Metformin Help Lower Insulin Resistance in Obese Children?

- Metformin has not shown consistent results in lowering insulin resistance among obese children.
- More research and controlled trials must be done to fully evaluate and describe metformin's effects on insulin resistance.

Is Metformin Safe for Treatment in Obese Children?

- All studies that analyzed safety of metformin found gastrointestinal side effects to be the main adverse effect. Since these symptoms are well known side effects of metformin, it is reasonable to consider metformin safe in pediatric patients 10 years and older.
- Dose adjustment was often successful in reducing GI symptoms and increasing overall tolerability of the drug.

Applicability to Clinical Practice

- Increasing numbers of overweight/obese pediatric patients will continue to be seen in primary care clinics
- Treatment can be challenging as there is no perfect protocol or recommendation proven completely effective
- This information allows healthcare providers to make an informed and evidence-based decision regarding the utilization of metformin as an adjunctive therapy
- Provides another option to consider when diet and exercise are not successful
- Age, gender, weight and pubertal status all play an important role in the decision to treat with metformin
- Appropriate dose and treatment length remains controversial

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References

Centers for Disease Control and Prevention. (2018). *Defining Childhood Obesity*. Retrieved from https://www.cdc.gov/obesity/childhood/defining.html

Hales, C., Carroll, M., Fryar, C., & Ogden, C. (2017). Prevalence of obesity among adults and youth: United States, 2015-2016. *NCHS Data Brief*. Retrieved from https://www.cdc.gov/nchs/data/databriefs/db288.pdf

Kyler, K., Kadakia, R., Palac, H., Kwon, S., Ariza, A., & Binns, H. (2018). Use of metformin for weight management in children and adolescents with obesity in the clinical setting. *Clinical Pediatrics*, 57(14), 1677–1685. http://dx.doi.org/10.1177/0009922818803404

Lentferink, Y., van der Aa, M., van Mill, E., Knibbe, C., & van der Vorst, M. (2018). Long-term metformin treatment in adolescents with obesity and insulin resistance, results of an open label extension study. *Nutrition & Diabetes*, 8(1), 1-10. http://dx.doi.org/10.1038/s41387-018-0057-6

Li, W., Li, M., & Kong, D. (2019). Clinical efficacy of metformin combined with lifestyle intervention for treatment of childhood obesity with hyperinsulinemia. *International Journal of Clinical and Experimental Medicine*, 12(6), 7644-7650. Retrieved from https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01980780/full

Marques, P., Limbert, C., Oliveira, L., Santos, M., & Lopes, L. (2016). 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*, 29(5), 1-8. http://dx.doi.org/10.1515/ijamh-2015-0110

Pastor-Villaescusa, B., Canete, M., Caballero-Villarraso, J., Hoyos, R., Latorre, M., Vazquez-Cobela, R., Plaza-Diaz, J., Maldonado, J., Bueno, G., Leis, R., Gil, A., Canete, R., & Aguilera, C. (2017). Metformin for obesity in prepubertal and pubertal children: A randomized controlled trial. *Pediatrics*, 140(1), 1-12. http://dx.doi.org/10.1542/peds.2016-4285

Scinta, W., & Morley, C. P. (2015). A retrospective chart study of a comprehensive medical weight loss approach to pediatric obesity: Initial results from the BOUNCE program. *Endocrinology & Metabolic Syndrome*, 4(2), 1-4. http://dx.doi.org/10.4172/2161-1017.1000173

Sun, J., Wang, Y., Zhang, X., & He, H. (2019). The effects of metformin on insulin resistance in overweight or obese children and adolescents: A PRISMA-compliant systematic review and meta-analysis of randomized controlled trials. *Medicine*, 98(4), 1-12. http://dx.doi.org/10.1097/MD.0000000000014249

van der Aa, M., Elst, M., van de Garde, E., van Mil, E., Knibbe, C., & van der Vorst, M. (2016). Long-term treatment with metformin in obese, insulin-resistant adolescents: Results of a randomized double-blinded placebo-controlled trial. *Nutrition & Diabetes*, 6(8), 1-10. http://dx.doi.org/10.1038/nutd.2016.37

Warnakulasuriya, L., Fernando, M., Adikaram, A., Thawfeek, A., Anurasiri, W., Silva, R., Sirasa, M., Rytter, E., Forslund, A., Samaranayake, D., & Wickramasinghe, V. (2018). Metformin in the management of childhood obesity: A randomized control trial. *Childhood Obesity*, 14(8), 553–565. http://dx.doi.org/10.1089/chi.2018.0043