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Effectiveness of metformin in preventing Type 2 diabetes in children and adolescents with overweight or obesity: A protocol for systemic review and meta-analysis

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Abstract:
A major global health concern is the increasing incidence of overweight and obesity in children and adolescents, which greatly raises the risk of Type 2 Diabetes Mellitus (T2DM) at a young age. A major contributing factor to the development of type 2 diabetes is insulin resistance, which is exacerbated by sedentary lifestyles, poor eating habits, and genetic susceptibility. Therefore, preventive measures are crucial, particularly in pediatric populations that are at high risk. Metformin has become a promising pharmaceutical option for postponing or preventing the onset of Type 2 diabetes in young people who are overweight or obese.

The biguanide class medication metformin is frequently used as a first-line treatment for adult Type 2 diabetes and is being researched more and more for its potential to prevent the condition in younger people. Reducing hepatic glucose synthesis, increasing peripheral glucose absorption, and boosting insulin sensitivity are its main modes of action. Metformin aids in treating insulin resistance in obese children and teenagers, which frequently exists prior to the development of diabetes.
Metformin's ability to stop pediatric populations from developing Type 2 diabetes from prediabetes has been assessed in a number of clinical trials and observational studies. The findings imply that metformin can considerably lower fasting blood glucose levels, enhance insulin sensitivity, and help with modest weight loss when paired with lifestyle changes including diet restriction and exercise. The chance of acquiring type 2 diabetes is reduced as a result of these combined effects.

Key Words: Rising Risk, Metformin , obesity, safety profile

I. Introduction:

Adolescent type 2 diabetes diagnoses have alarmingly increased due to childhood obesity, which has reached epidemic proportions globally [1]. Insulin resistance, obesity, and decreased physical activity all work together to cause metabolic dysfunction and hasten the onset of type 2 diabetes [2]. Traditionally, lifestyle adjustment (dietary alteration, etc.) has been the focus of preventive efforts for children and adolescents physical exercise, and controlling weight), yet in practical situations, sustained commitment and durability are difficult. For high-risk pediatrics groups, pharmacologic adjuncts such as metformin that enhance insulin sensitivity are therefore of interest [3].

Fig:1.1 This picture depicts about the condition of obesity

Metformin lowers the incidence of diabetes by about 30% in persons with impaired glucose tolerance [4]. However, because of differences in pathophysiology, glycemic trajectories, and treatment responses, young people are not "small adults." Additionally, there is a dearth of information on β-cell prevention and preservation in children [5]. Metformin is generally well tolerated and can improve weight and

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lipid profile, according to safety and dosage studies from adolescent populations, particularly in type 1 diabetes (T1D) as an adjuvant to insulin [6].
These studies provide information on safety and metabolic consequences pertinent to juvenile use, even if they focus on a different illness situation (T1D).
Additionally, the safety profile for insulin resistance and polycystic ovarian syndrome (PCOS) in adolescents is well-established; nevertheless, there is conflicting evidence about its effectiveness in avoiding or delaying type 2 diabetes [7].
Large kid prevention trials centered on incidence type 2 diabetes are generally sparse, despite biological plausibility and encouraging adult results. Despite the paucity of long-term data on diabetes prevention results, recent narrative and systematic reviews have emphasized the widespread use of metformin in the treatment of children obesity and insulin resistance [8].
Various results have been reported from individual studies in young populations; some have shown improvements in insulin sensitivity and fasting glucose, while others have shown no long-term benefit after stopping medication [9]. A thorough synthesis of the data is required because metformin is increasingly being used off-label to lower metabolic risk.
The pediatric data on metformin, with or without lifestyle modifications, for the prevention or postponement of type 2 diabetes in children and adolescents who are overweight or obese will be compiled in this systematic review. Using time-anchored outcome windows and defined diagnostic criteria, we will also look at changes in anthropometrics, adherence, insulin resistance, and glycemic control. This review attempts to guide clinical practice and the planning of upcoming pediatric preventive studies by elucidating the available data and its limitations.

Two essential components are necessary for the proper mapping, surveillance, and assessment of infectious diseases: (i) precise diagnostic techniques and (ii) effective population sampling tactics [10].

With an alarming rise in both adults and children and adolescents, type 2 diabetes mellitus (T2DM) has become a serious global public health concern. This rising tendency is mostly linked to the rising rates of obesity, sedentary lifestyles, and poor eating habits. (11)
Insulin resistance and decreased insulin production are hallmarks of type 2 diabetes mellitus, a long-term metabolic disease that raises blood sugar levels. Due to its long-term implications and rising disease burden, early onset of type 2 diabetes in young populations has become a major concern in recent years. (12)

The popular first-line oral antidiabetic medication metformin has drawn a lot of attention due to its possible use in both the prevention and treatment of Type 2 diabetes. It functions by increasing peripheral glucose absorption, decreasing hepatic glucose synthesis, and boosting insulin sensitivity. (13).

Maintaining long-term adherence in children and adolescents is frequently difficult, even though lifestyle modifications like diet restriction and physical activity remain the cornerstone of prevention. Thus, in high-risk populations, pharmaceutical therapies such as metformin are being investigated as supportive preventative measures. (14)

The usefulness of metformin in preventing or postponing the onset of Type 2 Diabetes in children and adolescents, however, is not well-established, despite encouraging results in adult populations. This emphasizes the necessity of doing a systematic review and meta-analysis in order to assess the current data critically and draw more precise conclusions (15).

Global health surveys state that over the past few decades, childhood obesity has become much more common, which has coincided with an increase in early-onset Type 2 diabetes (16).

One of the main underlying mechanisms in the development of Type 2 Diabetes is insulin resistance, which results in elevated blood glucose levels because the body's cells are unable to react to insulin (17).
Because early development of the condition may result in longer exposure to hyperglycaemia and an increased risk of problems in later life, children and adolescents are especially vulnerable (18).

Although lifestyle treatments continue to be the dominant strategy for prevention, poor adherence frequently limits their long-term efficacy, particularly in younger populations (19).
Metformin is a viable option for long-term use in preventative efforts among high-risk persons because it is usually regarded as safe and well-tolerated (20).

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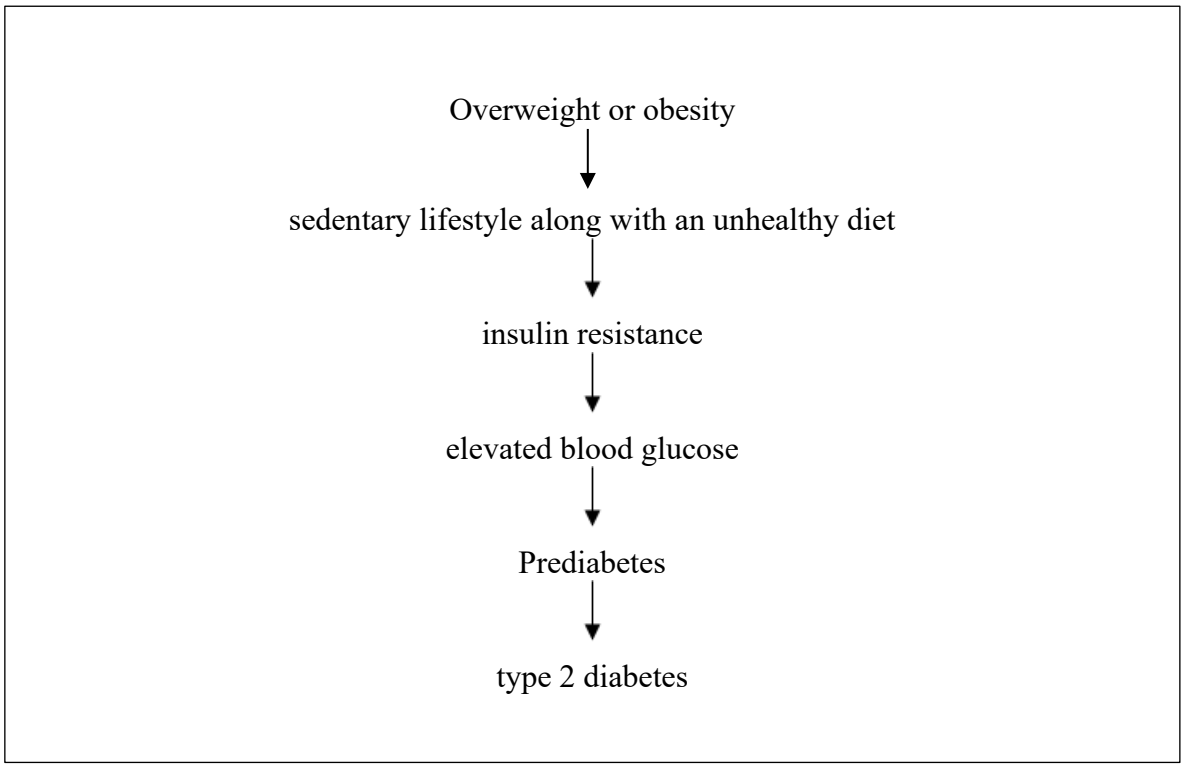
Pathogenesis of Type 2 Diabetes in Obese Children:



Risks associated with being overweight:
Being overweight increase the risk of a number of serious diseases and health conditions. Below is a list of said risks, according to the centers for disease control and prevention (CDC):

- High blood pressure
- Higher levels of LDL cholesterol, which is widely considered "bad cholesterol, "lower levels of HDL cholesterol, considered to be good cholesterol in moderation, and high levels of triglycerides.
- Type 2 diabetes.
- Coronary heart disease.
- Mental illness such as clinical depression, anxiety, and others.

Generally, a person should try to maintain a BMI below 25kg/m2, but ideally should consult their doctor to determine whether or not they need any changes to their lifestyle in order to be healthier.

Risks associated with being underweight:
Being underweight has its own associated risks, listed below:

- Vitamin deficiency, anemia (lowered ability to carry blood vessels).
- A disease that causes bone weakness, increasing the risk of breaking a bone.
- Possible reproduction issues for women due to hormonal imbalances that can disrupt the, menstrual cycle. Underweight women also have a higher chance of miscarriage in the first trimester.

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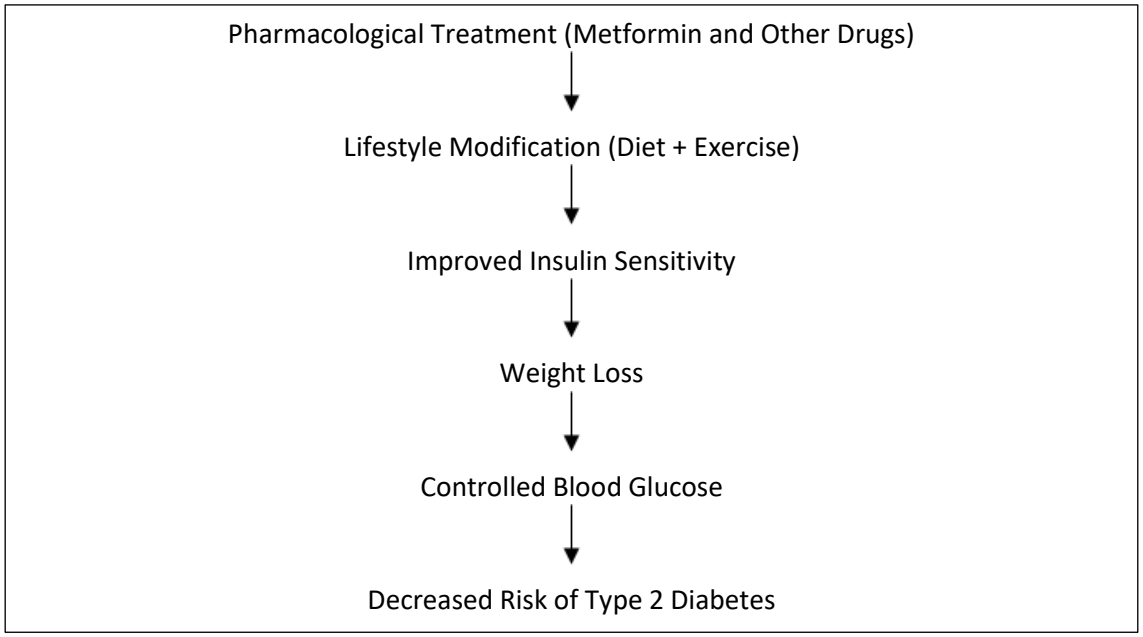
Prevention of Type 2 Diabetes



Factor:

1. **Age:** Childhood obesity raises the likelihood of adult obesity, and the highest rates of overweight and obesity are reached between the ages of 55 and 65.
2. **Energy intake:** Overeating results in obesity and weight increase**.**
3. **Sex:** Women have more body fat. The differences in prevalence of obesity vary in populations or among ethnic groups.
4. **Dietary fat intake:** According to ecological research, dietary fat and the prevalence of overweight are association.

Other drugs used in Prevention/Management of Type 2 Diabetes:

1. Orlistat: Adolescent obesity is treated with orlistat. It aids in weight loss, which lowers the chance of Type 2 diabetes.

Pharmacological Action: Orlistat stops the digestion and absorption of dietary lipids by inhibiting pancreatic and stomach lipases. About thirty percent of the fat that is consumed is eliminated undigested.

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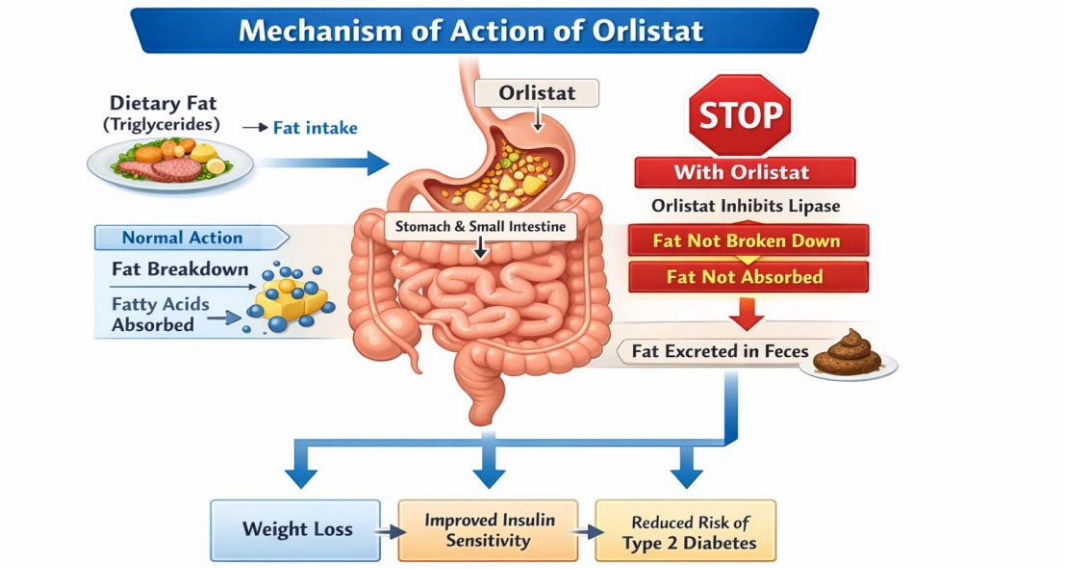
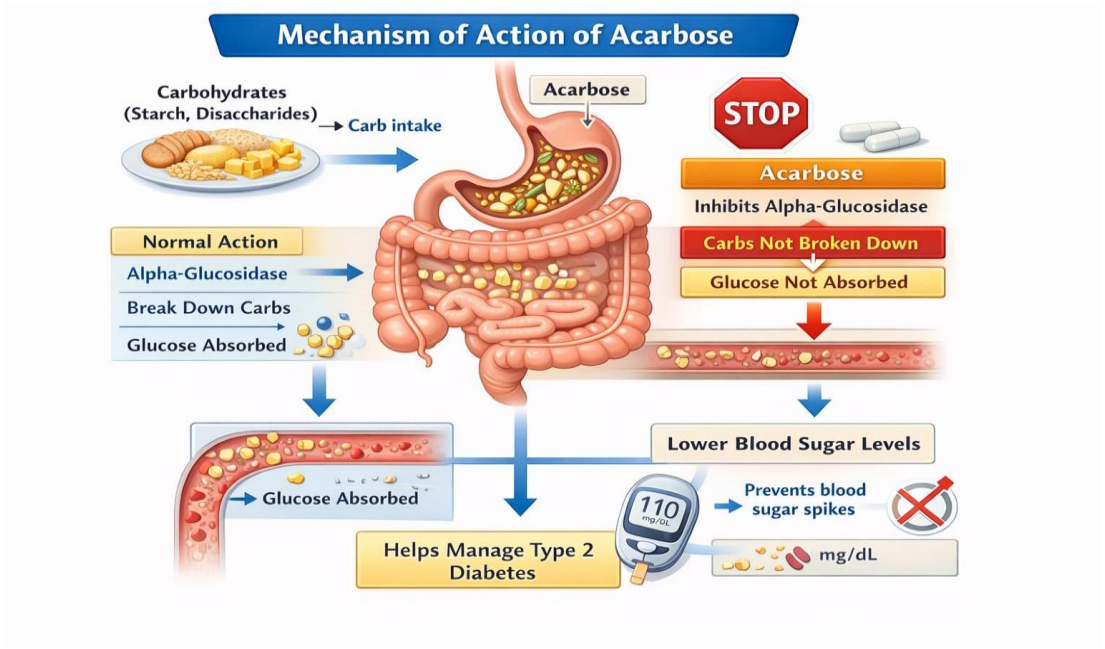


ADME:
Absorption: Systemic absorption is minimal.

Distribution: Poor absorption results in limited dissemination. Metabolism: The digestive system metabolizes
Excretion: Mostly eliminated by feces

2. Acarbose: Used to manage postprandial hyperglycemia in those who are susceptible to Type 2 diabetes.
Pharmacological Action: Acarbose delays the digestion of carbohydrates and the absorption of glucose by inhibiting the intestinal alpha-glucosidase enzymes.



ADME:
Absorption: The gastrointestinal tract's poor absorption . Distribution: Systemic distribution is minimal.

Metabolism: intestinal microorganisms are responsible for metabolism. Excretion: Mostly eliminated by feces.

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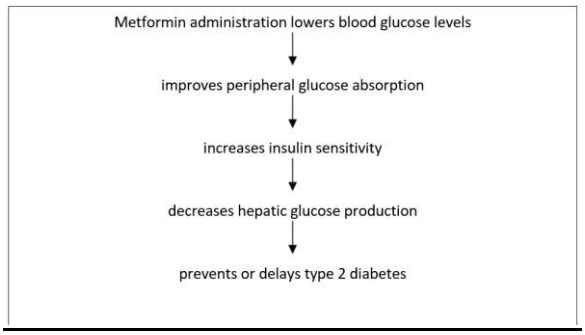
Although lifestyle adjustment is still the major strategy, these medications, together with metformin, help prevent and treat Type 2 diabetes, particularly in obese and high-risk adolescents.

Mechanism of Action of Metformin:



II. AIM & OBJECTIVE

In order to assess the efficacy and safety of metformin in preventing of Type 2 Diabetes Mellitus in overweight and obese juvenile populations, this study will methodically review and analyse the available scientific data.

1. To examine and compile published research on the usage of metformin in children.
2. To assess how well metformin works in preventing or postponing the onset of type 2 diabetes.
3. To evaluate how metformin affects body weight, blood glucose, and insulin resistance.
4. To evaluate metformin's safety and tolerability in kids and teenagers.
5. to assess how well metformin works in comparison to dietary and exercise changes.
6. To determine research gaps and recommend new study directions.

III. REVIEW OF LITERATURE

Zhao G. et al. (2022) Overall, the research that is currently available indicates that metformin helps children and adolescents who are obese lose weight and improve their insulin sensitivity. However, there is yet little solid proof of its ability to prevent Type 2 diabetes, and more extensive, long-term research is needed.

Masarwa R. et al. Systematic Review (2021), Metformin's efficacy in treating overweight and obese children and adolescents has been assessed in a number of trials. According to a systematic study, metformin lowers insulin resistance in juvenile populations and causes a little decrease in body mass index (BMI).

Rena G. et al. (2017). Patient compliance is another significant topic covered in the literature. According to studies, gastrointestinal side effects and the requirement for long-term treatment make it difficult for teenagers to stick to metformin medication. In real-world situations, poor compliance may restrict the drug's total efficacy.

***M. Fortes and associates (2014*).** Mechanisms of Action of Metformin. Additionally, recent studies have investigated how metformin affects gut flora. Improved metabolic outcomes have been linked to changes in the composition of the gut microbiome, indicating that metformin may indirectly affect glucose metabolism through gut-related pathways. Although research in this area is still ongoing, it offers a promising avenue for further study.

McDonagh MS et al. (2014), According to comparative research on anti-obesity medications indicates that although metformin has a better safety profile than other pharmacological treatments, its effectiveness in reducing weight is moderate.

Brufani C. et al. (2013), According to a review by metformin therapy for 6–12 months reduced BMI and enhanced insulin sensitivity in obese children without diabetes, while the long-term consequences are yet unknown.

***NS Glaser and associates (2011*),** Metformin and Adolescent Appetite Control. The early prevention of Type 2 Diabetes Mellitus in pediatric populations, especially in children and adolescents who are overweight or obese, has received more attention in recent publications. Pharmacological treatments like metformin are becoming more popular as a preventive measure due to the growing incidence of pediatric obesity.

Graham GG et al. (2011). Additionally, responses to metformin medication have been found to differ according to gender. According to certain research, teenage girls, particularly those with polycystic ovarian syndrome (PCOS), may improve their metabolic parameters and insulin sensitivity more than boys. This suggests that metformin's efficacy in pediatric populations may be influenced by hormonal variables.

Wilson DM et al. (2010), "Metformin Therapy in Insulin Resistant Youth," metformin affects energy metabolism and appetite management in addition to improving insulin sensitivity. Metformin has been shown to lower calorie intake via altering hypothalamic pathways, which may help adolescents stabilize their weight. Beyond its ability to decrease glucose, this method offers another benefit.

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Park MH et al. (2009), another meta-analysis of 38 research showed that metformin significantly lowers waist circumference, body weight, and BMI, suggesting its advantageous function in enhancing metabolic outcomes.

Srinivasan S. et al. (2006), additional long-term research is required to confirm metformin's significance in preventing Type 2 Diabetes, however prior clinical trials also indicated that it is somewhat helpful in lowering BMI and insulin resistance in obese children.

IV. Conclusion:

This systematic review and meta-analysis protocol aims to provide a structured and transparent method for evaluating existing evidence on obesity. The study is expected to generate reliable and comprehensive conclusions about the prevalence, risk factors, and health consequences of obesity. The results may support healthcare professionals, researchers, and policymakers in developing effective prevention strategies and treatment approaches to reduce the burden of obesity and improve public health outcomes.

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