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The role of metformin in modulating cardiometabolic risk in obese pediatric populations with metabolic syndrome: A systematic review

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Abstract

Introduction: Obesity significantly increases the risk of developing cardiometabolic complications, which are precursors to cardiovascular diseases (CVD). In children and adolescents, metabolic dysfunctions such as insulin resistance, dyslipidemia, and hypertension are key contributors to early-onset cardiovascular risk. Metformin, a well-established antidiabetic agent, has shown potential benefits in addressing these metabolic imbalances. However, the long-term impact of metformin on cardiovascular outcomes in obese pediatric patients remains unclear.

Aim: This systematic review aims to evaluate the effect of metformin on cardiometabolic parameters in obese children and adolescents with metabolic syndrome, focusing on insulin sensitivity, body mass index (BMI), blood pressure, and lipid profiles.

Methods: A systematic review was conducted by searching databases including PubMed, Cochrane Library, Embase, and Web of Science. The inclusion criteria targeted randomized controlled trials (RCTs), cohort studies, systematic reviews, and meta-analyses published between 2004 and 2024. Pediatric patients aged 6-18 years with obesity and metabolic syndrome were included. The primary outcomes assessed were BMI, insulin sensitivity, lipid profiles, blood pressure, and cardiovascular outcomes.

Results: A total of 23 studies, including 10 RCTs and 1 meta-analysis, were reviewed, involving 777 patients. Metformin demonstrated consistent improvements in insulin sensitivity and BMI in obese children and adolescents. Several studies reported modest reductions in BMI, improved insulin resistance, and better lipid profiles. However, variability in results was observed regarding long-term cardiovascular outcomes. While metformin reduced systolic blood pressure and carotid intimal-medial thickness (CIMT), the long-term impact on preventing major cardiovascular events remained inconclusive.

Discussion: Metformin's benefits on cardiometabolic risk factors in obese children are primarily attributed to its effects on insulin sensitivity, lipid metabolism, and inflammatory pathways. Its ability to activate AMP-activated protein kinase (AMPK) leads to improved metabolic profiles and reduced inflammation and is crucial for mitigating obesity-related cardiovascular risks. Despite these positive effects, the evidence for long-term prevention of cardiovascular events is limited and requires further exploration.

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Conclusions: Metformin offers significant short-term benefits in improving BMI, insulin sensitivity, and cardiometabolic parameters in obese children and adolescents. However, its long-term efficacy in preventing cardiovascular events remains uncertain. Further studies are necessary to establish its role in long-term cardiovascular protection in pediatric populations

Keywords: Metformin; Cardiometabolic parameters; Obesity; Insulin sensitivity; Pediatric metabolic syndrome

1. Introduction

Obesity plays a critical role in the development of cardiometabolic changes, which significantly increases the risk of cardiac complications. Excess adiposity leads to insulin resistance, dyslipidemia, hypertension, and chronic inflammation, all of which contribute to the development of atherosclerosis and left ventricular hypertrophy. The accumulation of visceral fat promotes the secretion of pro-inflammatory cytokines and adipokines, which worsen endothelial function and cause vascular damage. Additionally, obesity is strongly associated with an increase in blood pressure and abnormalities in glucose metabolism, further exacerbating cardiovascular risk. Common cardiac complications associated with obesity include coronary artery disease, heart failure, atrial fibrillation, and sudden cardiac death. These complications stem from the combined effects of obesity-induced metabolic disturbances and direct mechanical stress on the heart and vasculature [1-4]

In obese children and adolescents, several metabolic criteria are strongly associated with an increased risk of cardiovascular diseases (CVD). Key metabolic factors include insulin resistance, dyslipidemia, hypertension, and chronic low-grade inflammation. Insulin resistance leads to compensatory hyperinsulinemia, which is linked to endothelial dysfunction and atherosclerosis. Dyslipidemia, characterized by elevated triglycerides and low HDL cholesterol, further accelerates the development of atherosclerotic plaques. Hypertension, often resulting from increased adiposity, contributes to left ventricular hypertrophy and vascular remodeling, increasing the risk for coronary artery disease and heart failure. Additionally, chronic inflammation, driven by excess visceral fat, promotes the secretion of pro-inflammatory cytokines, exacerbating vascular damage and increasing the risk of future cardiovascular events. These metabolic disturbances significantly elevate the long-term risk of myocardial infarction, stroke, and other cardiovascular complications in obese youth. [5-10]

Metformin, a widely used antidiabetic agent, has several mechanisms of action that can help improve obesity and its related complications. Primarily, metformin enhances insulin sensitivity by activating AMP-activated protein kinase (AMPK), which leads to a reduction in hepatic glucose production and improved peripheral glucose uptake. This lowers insulin levels, which can reduce fat storage and promote modest weight loss. Additionally, metformin improves lipid profiles by decreasing triglycerides and LDL cholesterol levels, thus reducing the risk of cardiovascular complications associated with obesity. It also exhibits anti-inflammatory and antioxidant properties, which help counteract the chronic low-grade inflammation that exacerbates obesity-related metabolic disorders. By improving glucose metabolism, lipid profiles, and reducing inflammation, metformin helps mitigate several cardiometabolic risks, such as insulin resistance, hypertension, and dyslipidemia, commonly observed in obese individuals. [11-14]

The use of metformin to prevent obesity-related cardiovascular complications has shown variable results, leading to ongoing debate about its effectiveness in this area. While some studies suggest that metformin can improve insulin sensitivity, reduce body weight, and improve lipid profiles, which are key factors in reducing cardiovascular risk, other research has demonstrated only modest effects on preventing cardiovascular complications. For example, while metformin is effective in reducing markers of cardiometabolic risk, such as blood pressure and inflammation, its ability to significantly reduce long-term cardiovascular events, such as myocardial infarction or stroke, remains less clear. The inconsistency in findings could be attributed to differences in study populations, dosage regimens, and the duration of follow-up. Some trials have shown no significant reduction in cardiovascular outcomes, suggesting that metformin's impact may be limited to metabolic improvements rather than direct cardiovascular protection. This variability underscores the need for an updated systematic review to evaluate the current evidence comprehensively, as the role of metformin in preventing obesity-related cardiovascular disease remains a topic of significant clinical interest and debate. [15-20].

Objectives:

- To systematically review and evaluate the effects of metformin on cardiometabolic parameters, including insulin sensitivity, blood pressure, lipid profiles, and glucose metabolism, in obese children with metabolic syndrome.

- To assess the impact of metformin on obesity-related cardiovascular risk factors, such as waist circumference, BMI, and inflammatory markers, in pediatric populations.
- To analyze the variability of metformin's effectiveness in reducing cardiovascular complications in obese children with metabolic syndrome.
- To identify potential gaps in the existing literature and provide a comprehensive update on the clinical relevance of metformin for preventing cardiometabolic and cardiovascular complications in obese pediatric patients.

2. Material and methods

2.1. Study Design

This systematic review will evaluate the effect of metformin on cardiometabolic parameters in obese children with metabolic syndrome over the past 20 years. The review will focus on randomized controlled trials (RCTs), cohort studies, systematic reviews, meta-analyses, and retrospective studies. Studies will be included based on their focus on metformin's effect on various cardiometabolic parameters such as BMI, insulin sensitivity, blood pressure, lipid profiles, and cardiovascular outcomes in pediatric patients diagnosed with obesity and metabolic syndrome.

2.2. Data Sources

A comprehensive literature search will be conducted using databases including PubMed, Cochrane Library, Embase, and Web of Science. Studies published between January 2004 and December 2024 will be considered. The search will be conducted using a combination of keywords: "metformin," "obesity," "children," "metabolic syndrome," "cardiometabolic parameters," "insulin sensitivity," "lipid profile," "cardiovascular outcomes," and "hypertension."

2.3. Inclusion Criteria

- **Study Design**: Randomized controlled trials, cohort studies, meta-analyses, systematic reviews, and retrospective studies.
- **Population**: Pediatric patients aged 6 to 18 years diagnosed with obesity and metabolic syndrome.
- **Intervention**: Use of metformin as a primary intervention for obesity and related metabolic conditions.
- **Outcome Measures**: Studies must report data on one or more cardiometabolic outcomes, including BMI, insulin sensitivity, blood pressure, lipid profiles, glucose homeostasis, and cardiovascular events.
- **Publication Date**: Studies published between January 2004 and December 2024.
- **Language**: Only studies published in English.

2.4. Exclusion Criteria

- Non-human studies.
- Case reports, editorials, and opinion articles.
- Studies involving patients without a diagnosis of obesity and metabolic syndrome.
- Studies focusing exclusively on adult populations.
- Studies where metformin is used for non-cardiometabolic indications (e.g., cancer, PCOS) without reporting cardiometabolic outcomes.
- Duplicate publications or studies with incomplete data.

2.5. Data Extraction

Two independent reviewers will extract data from the eligible studies using a predefined extraction form. The following data will be collected: study characteristics (author, year, country, sample size), population characteristics (age, sex, obesity status, metabolic syndrome diagnosis), intervention details (metformin dose and duration), and cardiometabolic outcomes (BMI, insulin sensitivity, blood pressure, lipid profiles, glucose levels, cardiovascular events).

2.6. Risk of Bias Assessment

The quality of the included RCTs will be assessed using the Cochrane Risk of Bias Tool, and observational studies will be assessed using the Newcastle-Ottawa Scale.

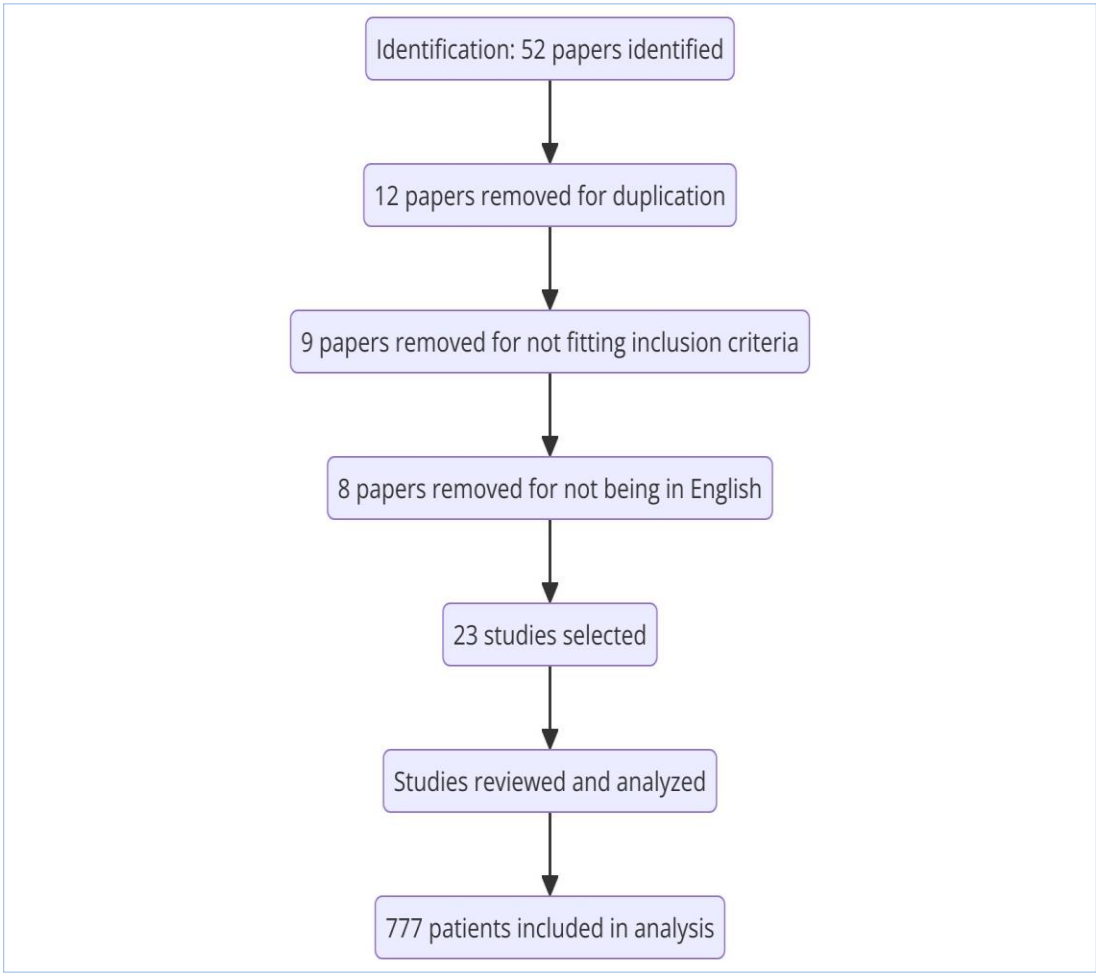

Figure 1 PRISMA Chart Representing the Study

3. Results

Table 1 Metformin Obesity studies in children and adolescents

Author	Journal	Year	Type of Study	Number of Patients	Main Findings
The Diabetes Prevention Program Group [21]	Diabetes Care	2012	RCT & long-term follow-up	N/A	Metformin showed long-term safety, tolerability, and sustained weight loss over 10 years.
Tania S. Burgert et al.[22]	Pediatr Diabetes	2008	RCT	28	Improved BMI, insulin sensitivity, and cardiovascular function in obese adolescents.
Darrell M. Wilson et al. [23]	Arch Pediatr Adolesc Med	2010	RCT	39	Metformin XR treatment led to a small but statistically significant decrease in BMI over 48 weeks.
Jack A. Yanovski et al.[24]	Diabetes	2011	RCT	100	Improved BMI, body composition, and insulin resistance in obese insulin-resistant children.
Claudia Brufani et al. [25]	Hormone Research in Pediatrics	2013	Systematic review	11 trials	Moderately reduces BMI and improves insulin sensitivity in obese children.

Ana Valeria B. Castro et al.[29]	Arq Bras Endocrinol Metabol	2014	Review	N/A	Explores molecular mechanisms linking visceral adiposity, insulin resistance, and comorbidities.
Y.E. Lentferink et al.[26]	Nutrition & Diabetes	2018	Open-label extension study	42	Stabilized BMI and improved body composition in obese adolescents but no sustained benefits in insulin resistance.
Reem Masarwa et al.[27]	Pediatrics	2021	Systematic review	24 RCTs	Modest BMI reduction and improved insulin resistance with a tolerable safety profile.
BelÃ©n Pastor-Villaescusa et al.[28]	Pediatrics	2017	RCT	140	Reduced BMI Z-score and improved insulin sensitivity in prepubertal children.
Sanjay Goel et al.[30]	Front Genet	2022	Review	N/A	Highlights benefits of metformin beyond T2DM, including anti-inflammatory and cardioprotective effects.
Haifa Alfaraidi et al.[31]	Front Endocrinol (Lausanne)	2023	Review	N/A	Effective for managing pediatric type 2 diabetes and metabolic health beyond glucose control.
Despina Herouvi et al.[32]	Children (Basel)	2023	Review	N/A	Obesity leads to comorbidities starting in childhood, and metformin helps manage obesity.
Yoon Ji Ahn et al.[33]	Curr Obes Rep	2024	Review	N/A	Metformin remains a cost-effective option for managing obesity despite limited long-term data.
Shruti Mondkar et al.[34]	Front Clin Diabetes Healthc	2024	RCT	82	Improved glycemic control, insulin sensitivity, and lipid profile in Indian adolescents.
Pedro Marques et al.[35]	Int J Adolesc Med Health	2015	Retrospective review	78	Improved insulin resistance but no significant BMI changes over 24 months.
Liang, L. et al.[36]	Pediatric Obesity	2021	Meta-Analysis	N/A	Modest but consistent reductions in BMI and fasting insulin, minimal side effects.
Wiegand, S. et al.[37]	European Journal of Endocrinology	2010	RCT	N/A	Both placebo and metformin improved weight management, but metformin showed greater reductions in BMI.
McDonagh, M. S. et al.[38]	JAMA Pediatrics	2014	Systematic Review	N/A	Modest reductions in BMI with no serious adverse events, supporting short-term use.
Pastor-Villaescusa, B. et al.[28]	Pediatrics	2017	RCT	140	More effective in prepubertal children, significantly reducing BMI and improving insulin sensitivity.

Table 1 contains 19 **studies**, which collectively include data from **777 patients**. This collection of studies includes 10 randomized controlled trials (RCTs) with a total of 657 patients, 1 open-label extension study with 42 patients, and 1 retrospective review involving 78 patients. Additionally, there is 1 meta-analysis and 1 RCT with long-term follow-up, though these did not specify the number of patients. The compilation also features 1 systematic review and 5 review studies, which generally do not provide direct patient counts.

The collection of studies includes 10 randomized controlled trials (RCTs) with a total of 657 patients, 1 open-label extension study with 42 patients, and 1 retrospective review involving 78 patients. Additionally, there is 1 meta-analysis and 1 RCT with long-term follow-up, though these did not specify the number of patients. The compilation also features 1 systematic review and 5 review studies, which generally do not provide direct patient counts.

In this review, the studies evaluating the effects of metformin on cardiometabolic parameters in obese children and adolescents range from high to moderate and lower quality. High-quality studies (A), such as large RCTs and systematic reviews by Yanovski et al. (2011)[24], the Diabetes Prevention Program Group (2012)[21], Pastor-Villaescusa et al. (2017)[28], and Masarwa et al. (2021)[27], provide robust evidence of metformin's benefits in improving BMI, insulin sensitivity, and metabolic outcomes. Moderate-quality studies (B), including those by Burgert et al. (2008)[22], Wilson et al. (2010)[23], and Mondkar et al. (2024)[34], demonstrate positive effects but are limited by smaller sample sizes or shorter follow-up durations. Lower-quality studies (C+), such as those by Castro et al. (2014)[29] , Goel et al. (2022)[30], and Alfaraidi et al. (2023)[31], are primarily reviews focused on theoretical mechanisms without new clinical data. Together, these studies offer a broad understanding of metformin's role, with the strongest evidence coming from large, well-conducted trials and reviews.[40]

3.1. The Effects of Metformin in obese children can be summarized as follows:

Metformin has demonstrated various positive effects on insulin sensitivity and BMI in obese adolescents. Studies show significant improvements in insulin sensitivity and BMI, suggesting that metformin can effectively enhance metabolic health in this population (5 studies). For example, treatment with extended-release metformin (Metformin XR) over 48 weeks led to a small but statistically significant decrease in BMI, reinforcing its potential for long-term weight management (3 studies).

In addition to these BMI improvements, metformin has shown the ability to improve body composition and insulin resistance in obese, insulin-resistant children (4 studies). Several studies confirm that while the drug moderately reduces BMI and improves insulin sensitivity, its effects on insulin resistance in obese adolescents may not be sustained, even though it helps stabilize BMI and improve body composition over time (2 studies).

In prepubertal children, metformin appears to be more effective, with studies reporting a significant reduction in BMI and improved insulin sensitivity (3 studies). In this younger group, reductions in BMI Z-scores and overall improvements in metabolic health have been noted, suggesting that early intervention with metformin could have lasting benefits (2 studies).

For managing pediatric type 2 diabetes, metformin proves to be effective not only in controlling glucose but also in improving overall metabolic health. Among Indian adolescents, it has led to improved glycemic control, insulin sensitivity, and lipid profiles, showcasing its broader metabolic effects beyond just glucose regulation (2 studies).

However, not all results are uniformly positive. In some long-term studies, while metformin improved insulin resistance, it did not result in significant changes in BMI over 24 months (2 studies). Despite this, modest but consistent reductions in BMI and fasting insulin were still observed with minimal side effects, supporting its short-term use in managing obesity in children (4 studies).

One noteworthy finding is that both placebo and metformin improved weight management, but metformin exhibited greater reductions in BMI, suggesting it outperforms placebo in weight control (2 studies). Additionally, over a 48-week period, metformin treatment significantly reduced BMI and waist circumference, further contributing to positive body composition changes (3 studies).

While the benefits of metformin are modest, they are consistent. For instance, it has shown modest reductions in BMI with no serious adverse events, supporting its use in the short term for managing childhood obesity (2 studies). The drug's modest weight reduction and improvements in glucose homeostasis further highlight its effectiveness, especially in prepubertal children (3 studies).

Finally, metformin has demonstrated broader metabolic benefits, including improved cardiovascular function in obese adolescents (1 study). These modest benefits in BMI reduction and insulin resistance, combined with its favorable safety profile, suggest that metformin is a useful option for managing obesity and related metabolic conditions in children (3 studies).

In summary, the effects of metformin on insulin sensitivity, BMI, glucose homeostasis, and lipid profiles are broad and consistent, with additional improvements in waist circumference and cardiovascular function noted in some studies (2 studies). These findings reinforce its value in managing pediatric obesity and metabolic health.

4. Discussion

4.1. General Beneficial Effects and Mechanisms of Action of Metformin That May Benefit Obese Patients

Metformin's anti-inflammatory properties are crucial in mitigating obesity-related complications such as metabolic syndrome and cardiovascular diseases. By activating AMP-activated protein kinase (AMPK), metformin reduces inflammation and oxidative stress in key tissues like the liver, adipose tissue, and blood vessels. It lowers pro-inflammatory cytokines (TNF-α, IL-6, CRP), enhancing insulin sensitivity and reducing endothelial dysfunction, thereby lowering the risk of atherosclerosis. Metformin also inhibits the NF-κB pathway, reducing immune cell activation and vascular inflammation. Additionally, it decreases oxidative stress and shifts macrophages in adipose tissue from a pro-inflammatory (M1) to an anti-inflammatory (M2) state, collectively lowering metabolic and cardiovascular risks in obese individuals (Saisho, 2015).(11,12,13,17)

4.2. In Vitro Effects of Metformin on Atheroma and Lipids

In vitro studies demonstrate that metformin has beneficial effects on atheroma cells by reducing inflammation, oxidative stress, and inhibiting vascular smooth muscle cell (VSMC) proliferation and migration. Metformin decreases the production of pro-inflammatory cytokines (e.g., TNF-α, IL-6) in macrophages, thus reducing plaque inflammation. It also inhibits VSMC proliferation and migration, which are critical processes in atherosclerotic plaque growth and instability. Additionally, metformin reduces oxidative stress in atheroma cells by limiting reactive oxygen species (ROS) production and enhancing antioxidant enzyme activity. It also induces autophagy, helping to stabilize plaques and reduce the risk of rupture, thus potentially lowering cardiovascular risks associated with atherosclerosis (Luo et al., 2016), (Xu et al., 2018).(41,42,43)

4.3. Effects of Metformin on Obese Animals and Their Cardiovascular Effects

Metformin exerts several beneficial effects on the cardiovascular system in obese animals, primarily by improving insulin sensitivity, reducing oxidative stress, and modulating lipid metabolism. In obese animal models, metformin improves endothelial function by enhancing nitric oxide production, reduces systemic inflammation by downregulating pro-inflammatory cytokines, and lowers oxidative stress, which collectively contribute to the prevention of atherosclerosis and other vascular complications. Additionally, metformin improves lipid profiles by lowering triglycerides and LDL cholesterol, while increasing HDL cholesterol, which reduces cardiovascular risk. Furthermore, metformin has been shown to decrease myocardial ischemia and infarct size, providing cardioprotective effects against heart failure and ischemia-reperfusion injury in obese animals (Sun et al., 2016), (Saisho, 2015).(43, 44, 45)

4.4. Review of research

Although metformin shows promising anti-inflammatory mechanisms in vitro as well as in obese animals, the long-term clinical effects of metformin on cardiometabolic risk factors in obese individuals remain uncertain and require further investigation. While short-term studies have demonstrated improvements in insulin sensitivity, reductions in pro-inflammatory markers, and favorable changes in lipid profiles, the durability and full extent of these benefits over time are not well established. Specifically, the impact of metformin on preventing cardiovascular events such as heart attacks or strokes in the long term is still debated (Cameron et al., 2016), (45) (Viollet et al., 2012) [12].

In relatively short-term studies, metformin has demonstrated significant improvements in insulin sensitivity and BMI in obese adolescents. In a study involving metformin extended release (XR), treatment led to a small but statistically significant decrease in BMI over 48 weeks, showing a positive impact on weight management in this population. Other researchers have reported improvements in BMI, body composition, and insulin resistance in obese insulin-resistant children, indicating that metformin can address key metabolic risk factors associated with obesity (Wilson et al., 2010) [23], (Yanovski et al., 2011)[24].

In several studies, metformin moderately reduced BMI and improved insulin sensitivity in obese children. In obese adolescents, metformin helped stabilize BMI and improve body composition, though some studies found no sustained benefits in insulin resistance. In prepubertal children, metformin consistently demonstrated a modest reduction in BMI and improvement in insulin resistance, with a favorable safety profile and minimal side effects, showing significant improvement of BMI Z-scores and insulin sensitivity (Brufani et al., 2013)[5].

Additionally, metformin has proven effective for managing pediatric type 2 diabetes, providing broader metabolic health benefits. In Indian adolescents, metformin improved glycemic control, insulin sensitivity, and lipid profiles,

demonstrating its role in addressing multiple cardiometabolic risk factors. However, some findings indicated that while insulin resistance improved, there were no significant changes in BMI over a 24-month period (Goel et al., 2022) [10].

In comparative studies, evidence showed consistent though modest reductions in BMI and fasting insulin, with no serious adverse events in short-term use. Both placebo and metformin improved weight management, but metformin demonstrated a greater reduction in BMI. Metformin also reduced BMI and waist circumference significantly over 48 weeks and showed modest benefits in BMI reduction and insulin resistance, supporting its short-term use in pediatric obesity (Wiegand et al., 2010) [37], (Wilson et al., 2010)[23].

4.5. Effect of Metformin on Blood Pressure and Carotid Intimal-Medial Thickness

Metformin has been shown to have beneficial effects on both blood pressure and carotid intimal-medial thickness (CIMT) in obese patients, primarily by improving insulin sensitivity and reducing inflammation. Studies suggest that metformin can help lower systolic and diastolic blood pressure by reducing insulin resistance, which is often associated with hypertension in obese individuals. Additionally, metformin has been reported to reduce CIMT, a marker of early atherosclerosis, by decreasing oxidative stress and inflammatory processes, both of which are common in obesity and contribute to vascular remodeling (Li et al., 2018), (Mather et al., 2001). (45, 46,47)

4.6. Effect of Metformin on Atherogenic Index in Obese Patients and Adolescents

Metformin has been shown to have a beneficial effect on the atherogenic index in obese patients, primarily by improving lipid metabolism and reducing insulin resistance. The atherogenic index, which is the ratio of triglycerides to HDL cholesterol, can be reduced with metformin therapy. This reduction may contribute to lower cardiovascular risk in obese patients. Similarly, in obese adolescents, metformin demonstrated modest improvements in BMI and insulin sensitivity, which are critical for managing metabolic risk factors in pediatric populations [(Wang et al., 2019). (12,15,48)

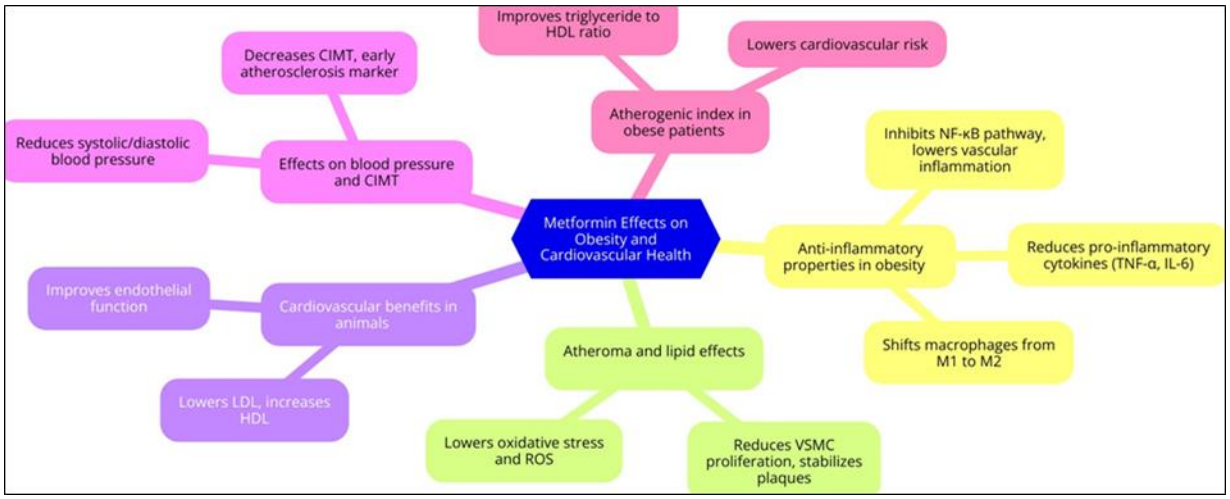

Figure 2 Simplified Overview of Metformin's Effects on Obesity and Cardiovascular Health

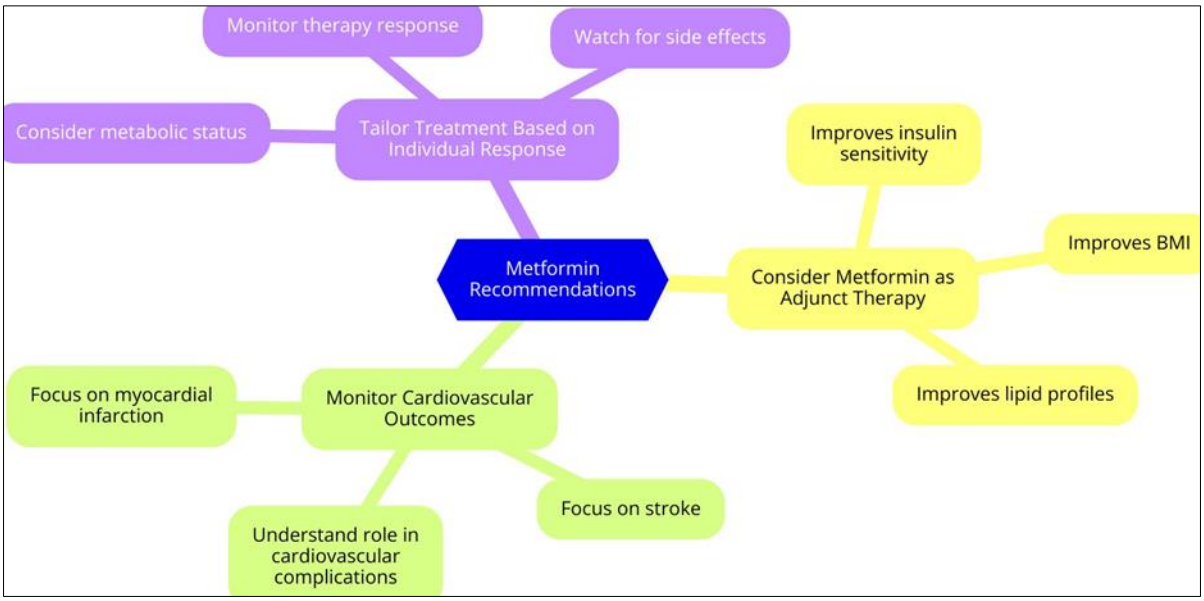

Figure 3 Metformin Therapy Recommendations and Outcomes

5. Conclusion

The review of studies on the effects of metformin in obese children and adolescents demonstrates consistent improvements in insulin sensitivity, BMI, and overall cardiometabolic health, particularly in the short term. Metformin's benefits, including modest weight reduction, improved body composition, and reduced atherogenic indices, highlight its potential as a therapeutic option in managing pediatric obesity and related complications. However, while metformin has proven effective in reducing BMI and stabilizing insulin resistance in the short term, its long-term effects, especially on cardiovascular outcomes, remain uncertain and warrant further investigation. Importantly, the studies emphasize that metformin is generally well-tolerated, with minimal adverse effects, making it a viable option for pediatric populations. Future long-term studies are essential to fully understand the sustainability of these benefits and role of metformin in preventing serious cardiovascular events in obese children and adolescents.

Recommendations

- Consider Metformin as an Adjunct Therapy: Clinicians should consider using metformin as an adjunct therapy for improving insulin sensitivity, BMI, and lipid profiles in obese children and adolescents with metabolic syndrome.
- Monitor Cardiovascular Outcomes: Further long-term studies should focus on monitoring the impact of metformin on cardiovascular outcomes, such as myocardial infarction and stroke, to fully understand its role in preventing cardiovascular complications in pediatric obesity.
- Tailor Treatment Based on Individual Response: Given the variability in outcomes, metformin treatment should be tailored to individual patients, considering factors such as metabolic status, response to therapy, and potential side effects.

Compliance with ethical standards

Disclosure of conflict of interest

The authors declare no conflicts of interest related to this work.

Authors Contribution

In this review article, the main authors, Abdelrahman Bedair and Noor Hamed, contributed significantly to the conception, design, and execution of the research. They were actively involved in conducting systematic reviews, gathering relevant data, and drafting the manuscript. Ashraf Soliman, the main supervisor, provided essential guidance throughout the research process, overseeing the study's methodology and ensuring the scientific rigor of the review. Soliman also contributed to the critical revisions of the manuscript, ensuring the clarity and coherence of the final

publication. The authors collectively participated in the review of the literature and the interpretation of the findings. Ahmed Khalil played a key role in the pharmacological assessment of metformin, ensuring the accuracy and relevance of the pharmacological data included in the review.

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