Luo Y F and Mireguli M (2023) EFFICACY AND SAFETY OF METFORMIN AND INSULIN COMBINATION THERAPY IN TYPE 1 DIABETIC CHILDREN: IMPACT ON PHYSICAL FITNESS AND GAME PARTICIPATION. Revista Internacional de Medicina y Ciencias de la Actividad Física y el Deporte vol. 23 (93) pp. 360-373.
DOI: https://doi.org/10.15366/rimcafd2023.93.023

ORIGINAL

EFFICACY AND SAFETY OF METFORMIN AND INSULIN COMBINATION THERAPY IN TYPE 1 DIABETIC CHILDREN: IMPACT ON PHYSICAL FITNESS AND GAME PARTICIPATION

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Recibido 18 de agosto de 2022 **Received** August 18, 2022
Aceptado 23 de octubre de 2023 **Accepted** October 23, 2023

ABSTRACT

Objective: This study aims to systematically evaluate the efficacy and safety of metformin combined with insulin therapy in managing type 1 diabetes mellitus (T1DM) in children. It particularly focuses on the impact of this combination therapy on physical fitness and game participation, providing an evidence-based reference for clinical treatment. **Methods:** A comprehensive search was conducted in databases including PubMed, Cochrane Library, Embase, Clinical Trials, CNKI, and Wanfang Data library, covering all publications up to May 2022. The selection criteria focused on randomized controlled trials examining the use of metformin and insulin in combination for treating children with T1DM. Data analysis was carried out using Revman5.40 software. **Results:** A total of 17 studies meeting the inclusion criteria were analyzed in this meta-analysis, encompassing 1119 children with T1DM. The analysis revealed no significant difference in blood glucose levels, body quality index, total adverse reaction events, or impact on physical fitness and game participation between the study and control groups. Notably, the study group exhibited significantly lower fasting blood glucose levels, 2-hour postprandial blood glucose levels, glycosylated hemoglobin levels, and daily insulin dosage, along with a shortened time to reach glycemic targets. However, the risk of gastrointestinal adverse reactions was notably higher in the study group. **Conclusion:** The combination of metformin and insulin in treating children with T1DM shows significant benefits in controlling blood glucose levels and reducing daily insulin requirements, potentially supporting better physical

fitness and game participation. However, the increased risk of gastrointestinal adverse reactions warrants careful monitoring and management in clinical practice.

KEYWORDS: Physical games; Type 1 diabetes; Efficacy; Safety; Meta-analysis, Fitness

1. INTRODUCTION

Type 1 Diabetes Mellitus (T1DM) is a chronic autoimmune disorder predominantly diagnosed in children and adolescents, characterized by the destruction of insulin-producing beta cells in the pancreas(Wu, Lu, Yang, & Zhang, 2021). This condition necessitates life-long insulin therapy to manage blood glucose levels and prevent acute and long-term complications (Song et al., 2022).

However, the management of T1DM in pediatric populations presents unique challenges, particularly concerning the maintenance of optimal glycemic control and the minimization of adverse effects, which are essential for promoting normal growth, development, and quality of life(Rashidi, Ghaderian, Latifi, & Hoseini, 2017). Recent advancements in diabetic care have explored the combination of insulin with oral hypoglycemic agents, such as metformin, to improve glycemic control. Metformin, primarily used in Type 2 Diabetes Mellitus (T2DM), has been considered for T1DM due to its potential benefits in insulin sensitivity, weight management, and possibly cardiovascular health(Atkinson & Eisenbarth, 2001; Jayaraman, Lau, & Ng, 2018). This emerging therapeutic strategy has garnered attention for its potential to reduce insulin doses, improve metabolic control, and possibly enhance physical activity tolerance in children with T1DM(Soliman, De Sanctis, Alaaraj, & Hamed, 2020).

Physical fitness and active participation in games and sports are vital for children's overall health and well-being. For children with T1DM, these activities are not only integral to their lifestyle but also present an additional layer of complexity in diabetes management. The balance between insulin therapy, dietary intake, and physical activity is critical to prevent hypo- or hyperglycemic episodes, which can be immediate barriers to physical activity participation(Alotaibi, Al Khalifah, & McAssey, 2020).

This study aims to systematically evaluate the efficacy and safety of metformin combined with insulin in the treatment of children with T1DM. It particularly focuses on the impact of this therapy on physical fitness and game participation, which are key components of pediatric health and development. By analyzing data from randomized controlled trials, this research seeks to provide an evidence-based reference for clinical treatment decisions and to explore how this combination therapy might influence the daily lives and activity levels of children with T1DM.

2. Materials and methods

2.1 Sources

PubMed, Cochrane library, Embase, Clinical Trials, CNKI, and Wanfang Data library were searched for the keywords "metformin", "type 1 diabetes", and "children". The last search was conducted on May 31, 2022.

2.2 Inclusion and exclusion of literature

2.2.1 Inclusion criteria

Published clinical studies on the treatment of children with type 1 diabetes with insulin combined with metformin; subjects were children; the study group was treated with insulin combined with metformin and the control group was treated with insulin combined with placebo or placebo; the study results included data on the effectiveness and safety of the treatment:(1)glycated hemoglobinA1C (HbA1c);(2)fasting blood glucose (FBG);(3)postprandial 2h plasma glucose (2h PPG);(4)time of blood glucose reaching the standard (TBGRS);(5)body mass index (BMI);(6)total insulin daily dose (TIDD);(7)Total adverse events (TAEs);(8)Hypoglycemia events (HEs);(9)Ketoacidosis events (KEs);(10)Gastrointestinal adverse reaction events (GIAREs).

2.2.2 Exclusion criteria

Duplicate reports, poorly described data and those containing only abstracts from congress meetings; subjects who were not children, type 2 diabetics.

2.3 Criteria for assessing the quality of the literature

The quality assessment criteria recommended by the Cochrane Handbook of Evaluation 5.3(Higgins et al., 2011) were used, including five items: (1) whether random allocation methods were applied; (2) whether allocation protocols were concealed; (3) whether study subjects, treatment protocol implementers, and study outcome measures were blinded; (4) whether baselines were comparable;(5) other sources of bias.

2.4 Statistical processing

RevMan 5.4 software provided by the Cochrane Collaboration Network was applied for systematic evaluation analysis. All outcome variables were transformed into standard units. Continuous variables (e.g. fasting blood glucose) were analysed using weighted mean difference (WMD) and its 95% confidence interval (95% CI) as the efficacy analysis statistic; count data (e.g. hypoglycaemic events, ketoacidotic events) were analysed using relative risk

(RR) and 95% CI as the efficacy analysis statistic. If there was no significant clinical heterogeneity between studies (I^2<50%, P>0.1), Meta-analysis was performed using a fixed-effects model; if I^2≥50%, indicating that there was clinical heterogeneity among the studies in each group, Meta-analysis was performed using a random-effects model. Possible publication bias was analysed using funnel plots. Possible publication bias was analyzed using funnel plots. Funnel plots are graphical representations that can help assess the potential for bias or systematic differences in study results. These methodological steps adhere to common practices in systematic reviews and meta-analyses, ensuring rigorous and standardized procedures for the analysis of clinical trial data.

3. Results

3.1 Results of the literature search

According to the inclusion and exclusion criteria, a total of 17 studies finally met the inclusion criteria and were included in the Meta analysis. There were 1119 children with type 1 diabetes, including 577 cases in the insulin combined with metformin treatment group and 542 cases in the placebo or insulin alone treatment group. The flow chart of the literature retrieval is shown in Figure 1, the basic information of the included studies is shown in Table 1.

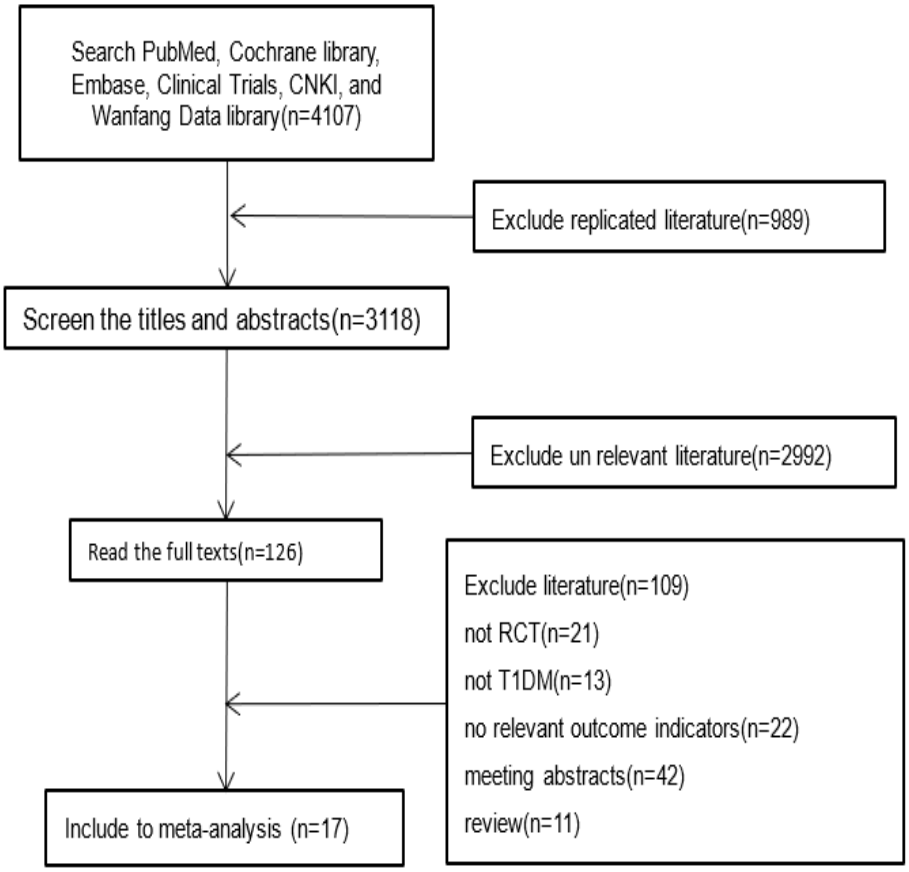

Figure 1: Flow of literature retrieval

Table 1: Basic characteristics of 17 eligible studies

STUDY	YEAR	PATIENTS N	AGE RANGE	INTERVENTION		FOLLOW-UP MONTHS	OUTCOME INDEX
		STUDY/ CONTROL		STUDY	CONTROL		
(Särnblad, Kroon, & Åman, 2003)	2003	13/13	14-20	Insulin+ Metformin	placebo	3M	①⑤⑥
(Hamilton, Cummings, Zdravkovic, Finegood, & Daneman, 2003)	2003	14/13	12-17	Insulin+ Metformin	placebo	3M	①⑤⑥
(Pan Q, 2011)	2011	30/22	12-17	Insulin+ Metformin	Insulin	3M	①②③④⑥⑧
(Codner et al., 2013)	2013	25/23	12-17	Insulin+ Metformin	placebo	9M	①⑤⑥
(Libman et al., 2015)	2015	71/69	12-18	Insulin+ Metformin	placebo	6M	①⑥⑦⑧⑨⑩
(Nadeau et al., 2015)	2015	40/40	13-18	Insulin+ Metformin	placebo	6M	①⑤⑥⑩
(Nwosu et al., 2015)	2015	15/13	10-20	Insulin+ Metformin	placebo	9M	①⑤⑥⑧
(Anderson et al., 2017)	2017	45/45	8-18	Insulin+ Metformin	placebo	12M	①⑥⑦⑧⑨⑩
(Dong J 2017)	2017	66/60	10-14	Insulin+ Metformin	Insulin	3M	②④⑥
(Bjornstad et al., 2018)	2018	24/24	12-18	Insulin+ Metformin	placebo	3M	①⑤⑥⑦
(Zhao Y, 2018)	2018	34/36	10-14	Insulin+ Metformin	Insulin	3M	②③④⑥
(Cree-Green et al., 2019)	2019	19/18	12-18	Insulin+ Metformin	placebo	3M	①⑥⑦⑨⑩
(Kang CJ, 2020)	2020	47/47	5-14	Insulin+ Metformin	Insulin	3M	①②⑥⑧⑨
(Gourgari et al., 2021)	2021	25/10	12-20	Insulin+ Metformin	placebo	6M	①⑤⑥
(Elbarbary, Ismail, & Ghallab, 2022)	2022	40/40	12-18	Insulin+ Metformin	placebo	6M	①②⑥
(Sheikhy et al., 2022)	2022	25/25	12-18	Insulin+ Metformin	placebo	9M	①⑥
(Liu ZJ, 2022)	2022	44/44	9-16	Insulin+ Metformin	Insulin	3M	②③④⑥⑦

3.2 Results of the methodological quality evaluation

All 17 included studies(Hamilton et al., 2003; Särnblad et al., 2003) specified the specific method of randomisation,7 studies (Bacha & Klinepeter Bartz, 2016)did not describe the method of allocation concealment,2studies (Codner et al., 2013)did not describe the blinding method in detail,1 study (Libman et al., 2015) didn't have complete outcome data; 7 studies (Nadeau et al., 2015)other risks of bias were unclear(Nwosu et al., 2015). The results of the methodological quality assessment are shown in Figures 2 and 3(Anderson et al., 2017).

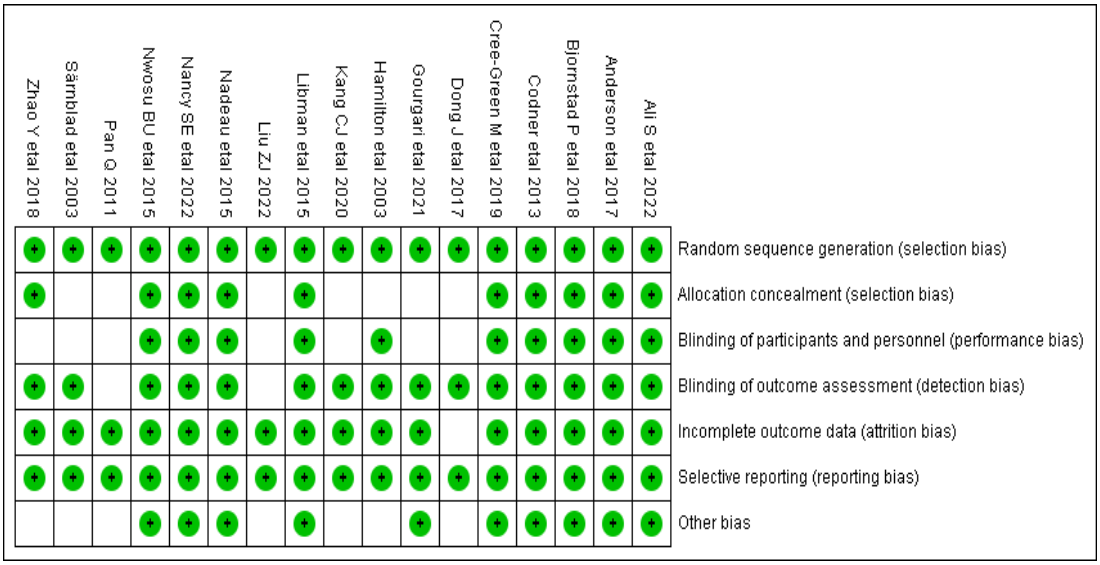

Figure 2: General diagram of risk of bias

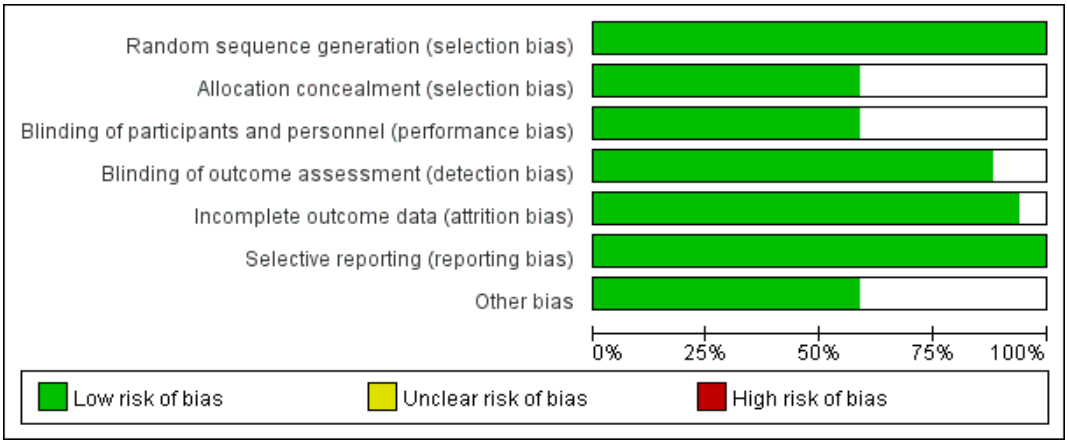

Figure 3: Risk of bias bar chart

4. Meta-analysis results

4.1 Comparison of Efficacy

(i) Effect of insulin combined with metformin therapy on glycaemic control in children with type 1 diabetes: 17 studies all provided glycemic control

outcomes in 2 groups, among which 6 studies provided fasting glucose data; 3 studies provided 2h postprandial glucose data. 4 studies provided time of blood glucose reaching the standard data, and 14 studies provided glycated hemoglobin data(Dong, Huang, & Zhao, 2017). The results of the heterogeneity test suggested that the included studies were heterogeneous, and the random-effects model was used to analyze. Meta-analysis showed that the fasting blood glucose level in the study group was lower than that in the control (Bjornstad et al., 2018)group(OR=-1.36,95% CI:-2.47~-0.25,Z.=2.40,P=0.02).There was no significant difference in blood glucose level 2 hours after meal between the two groups(OR=-1.63,95%CI: -4.82~1.56,Z=1.00,P=0.32) (Nally, Sherr, Van Name, Patel, & Tamborlane, 2019). The time of reaching the standard of blood glucose of the study group was shorter than that of the control group (OR=-3.48,95% CI: -5.10~-1.86, Z=4.21,P＜0.0001) ,and the level of glycosylated hemoglobin was significantly lower than that of the control group(OR =-0.94,95% CI:-1.40~-0.47,Z=3.93,P＜0.0001),See Figure 4.

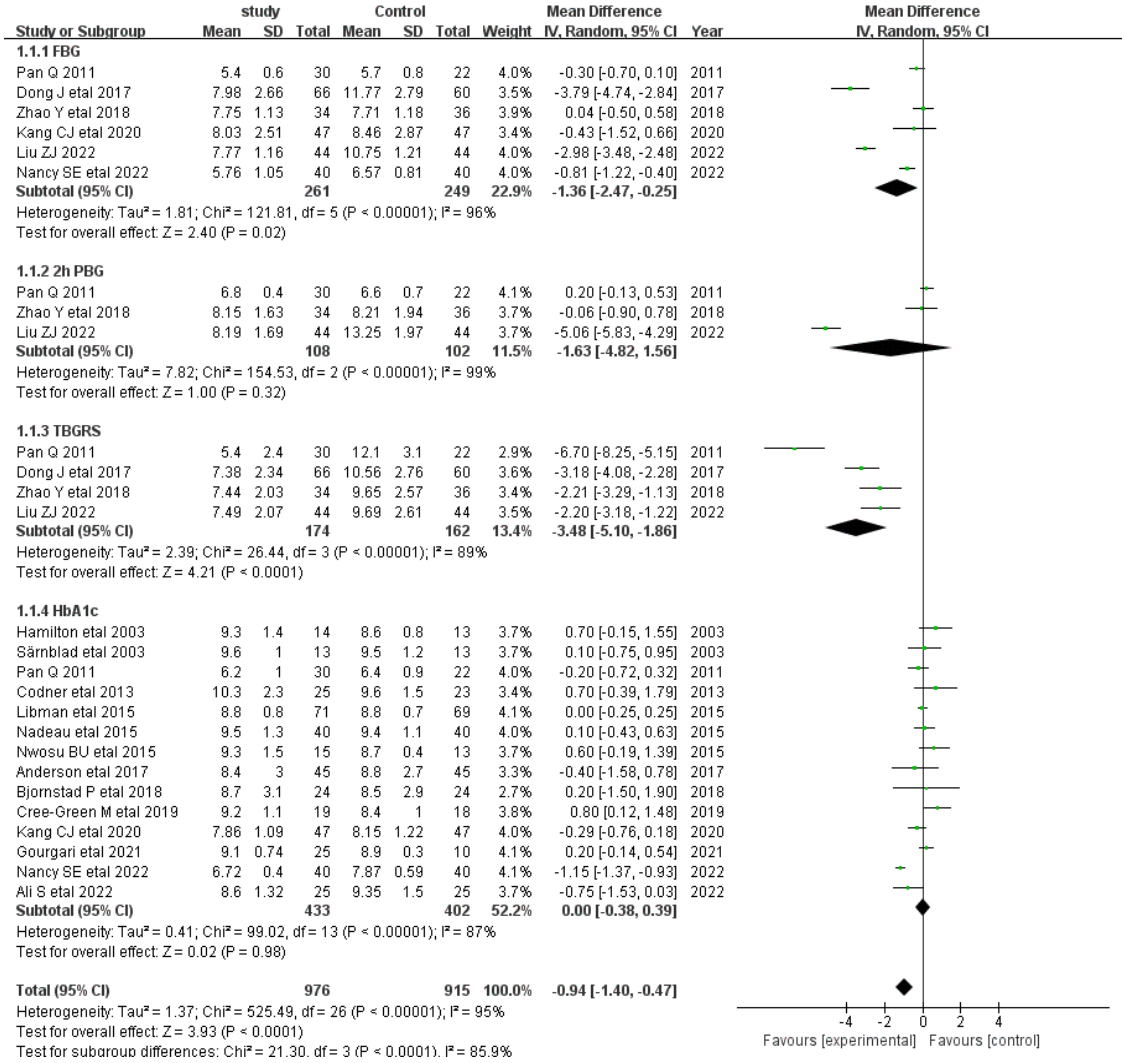

Figure 4: Forest plot for meta-analyses comparing study group with control group in blood glucose controlling WMD. weighted mean difference

(ii) The effect of insulin combined with metformin treatment on body mass index in children with type 1 diabetes mellitus: Seven of the 17 RCTs studies provided improvements in body mass index. There was no statistical heterogeneity between studies (P=0.32,I^2=14%) and analysis was performed using a fixed effects model(Cree-Green et al., 2019). The results showed no statistically significant difference in glycaemic control in the insulin combined with metformin treatment group compared with the control group (OR=-0.86,95% CI: -1.76 ~ 0.04, Z=1.88, P= 0.06), see Figure 5.

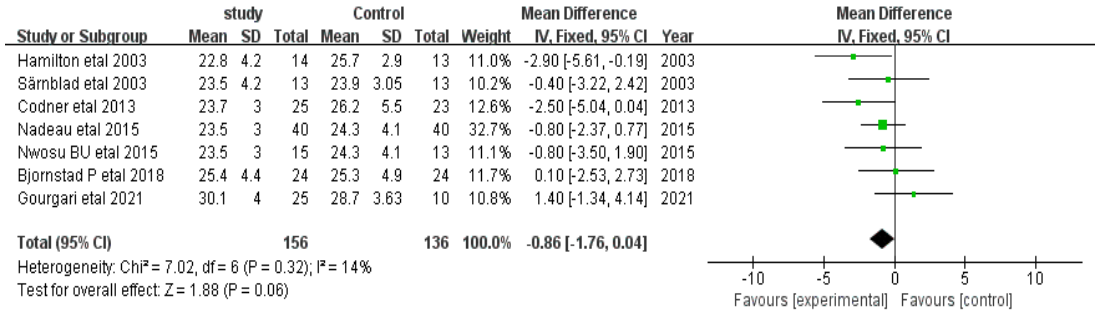

Figure 5: Forest plot for meta-analyses comparing study group with control group in BMI WMD. weighted mean difference

(iii) Effect of insulin combined with metformin therapy on daily insulin dosage in children with type 1 diabetes mellitus: All 17 included RCTs compared the daily insulin dosage between the two groups of patients. The results of the heterogeneity test suggested heterogeneity in the included studies (P<0.0001, I^2= 69%), and were combined for analysis using a random effects model(C. Liu, Wu, Zheng, Li, & Li, 2015). The results showed that the daily insulin dosage was significantly lower in the study group than in the control group (OR=-0.41,95%CI: -0.64~-0.19, Z=3.58, P=0.0003), see Figure6.

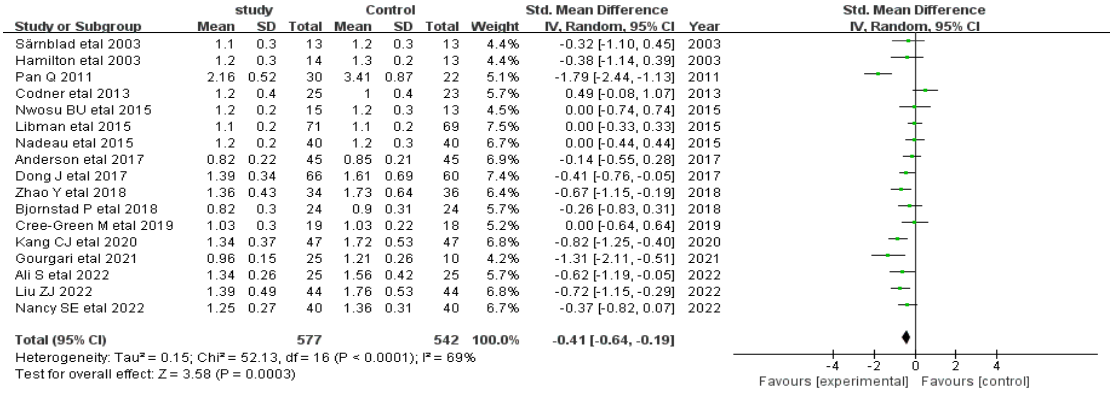

Figure 6. Forest plot for meta-analyses comparing study group with control group in total daily insulin dose WMD. weighted mean difference

4.2 Comparison of safety

All 17 studies provided data on adverse reactions in 2 different treatment

regimens. 5 studies provided data on total adverse events, 5 studies provided data on hypoglycaemic events, 4 studies provided data on ketoacidosis events and 4 studies provided data on gastrointestinal adverse events. Meta-analysis showed that the differences in total adverse events, hypoglycaemic events and ketoacidosis events were not statistically significant in the study group compared with the control group (total adverse events: RR = 1.33, 95% CI: 0.69-2.56, Z = 0.86, P = 0.39; hypoglycaemic events: RR = 0.69, 95% CI: 0.15-3.23, Z = 0.48, P = 0.63; ketoacidosis events: RR = 1.28, 95% CI: 0.57-2.90, Z = 0.60, P = 0.55), but Gastrointestinal adverse events were significantly higher than in the control group (RR =1.74,95% CI :1.32~2.29,Z =3.93,P<0.0001), see Figure 7.

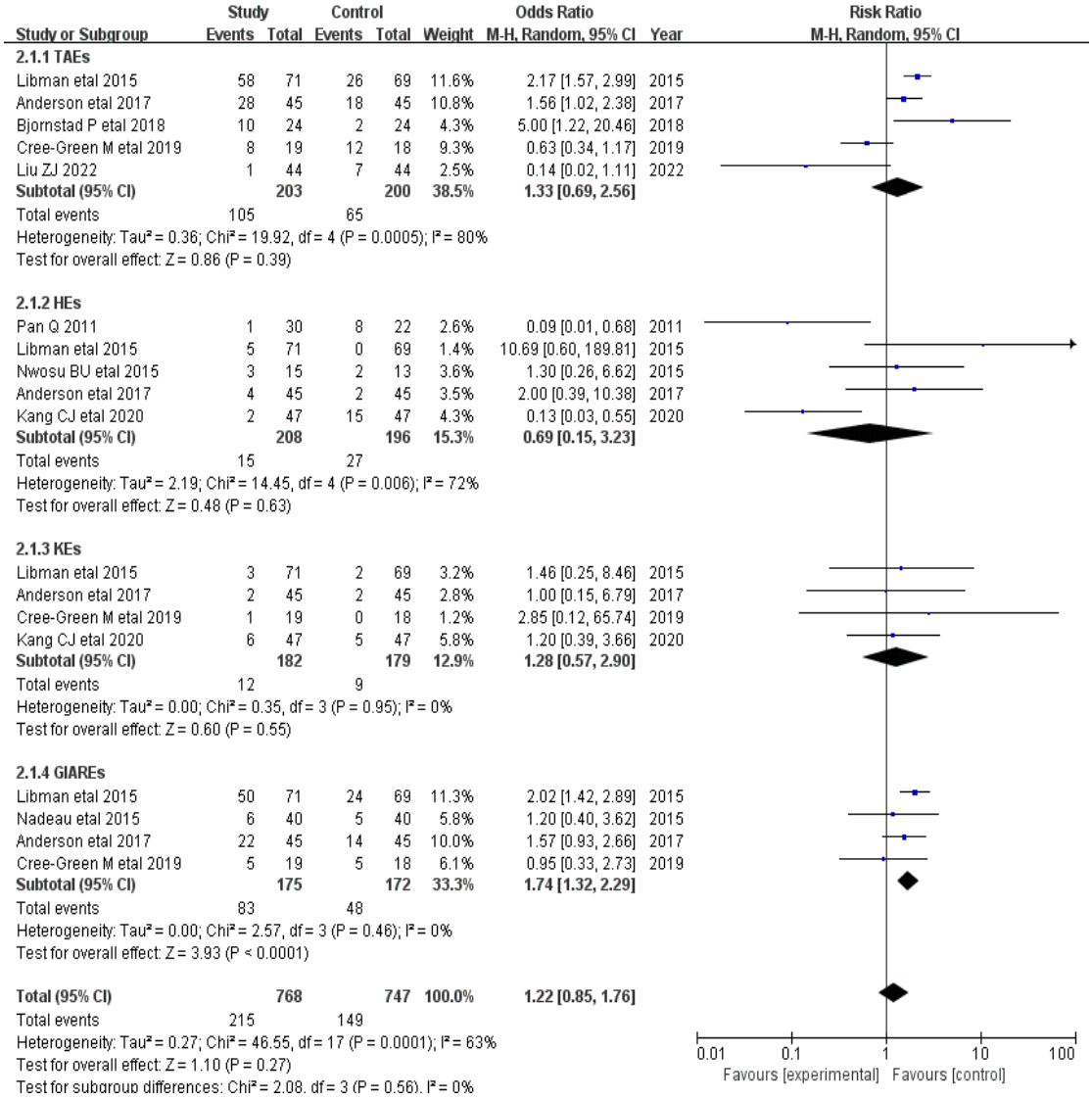

Figure 7: Forest plot for meta-analyses comparing study group with control group in terms of adverse events during the treatment

4.3 Publication bias analysis

Use TIDD as the indicator to draw a funnel chart for bias analysis. The

results show that the studies are scattered and symmetrical, indicating that there is no publication bias. See Figure 8.

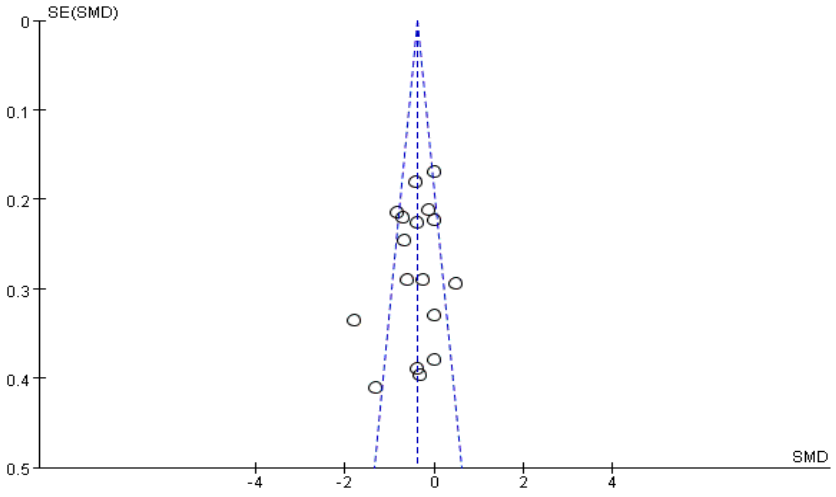

Figure 8: Funnel plot of the TIDD

5. Discussion

Metformin inhibits hepatic glucose output, increases skeletal muscle uptake and utilization of glucose, and improves insulin sensitivity. In recent years, insulin combined with metformin has been tried by physicians for the treatment of type 1 diabetes. Liu Y et al (Y. Liu et al., 2022) conducted a Meta-analysis of 10 overseas clinical studies of metformin in combination with insulin in children with type 1 diabetes mellitus. The results showed that the combined treatment could significantly improve glycosylated hemoglobin, reduce BMI and daily insulin consumption in children with type 1 diabetes (Adib, BARAKAT, MASRI, SABOUR, & CAPAPÉ, 2021).

The results of this study are consistent with that of glycosylated hemoglobin and daily insulin dosage. In addition, this study also found that metformin combined with insulin can improve fasting blood glucose and reduce the time of reaching the standard of blood glucose, but it does not support the improvement of BMI. Five studies in Chinese children with type 1 diabetes were included in this Meta-analysis, which is more relevant for the treatment of children with type 1 diabetes in China. Regarding the safety of metformin combination therapy, Liu Y et al (Y. Liu et al., 2022) showed that the incidence of hypoglycaemic events and the risk of gastrointestinal adverse effects were significantly higher in children in the insulin and metformin combination therapy group. This result shows that the gastrointestinal reaction of children with type 1 diabetes in the insulin and metformin combined treatment group is significantly increased, but it does not support the correlation between metformin and hypoglycemic events. Therefore, when trying to add metformin to children with type 1 diabetes, close attention should be paid to

gastrointestinal reactions such as diarrhea and nausea to reduce or avoid adverse events (Cherfan, Avgerinos, & Chaer, 2020).

6. Conclusion

The present meta-analysis provides substantial evidence supporting the efficacy of metformin combined with insulin therapy in managing Type 1 Diabetes Mellitus (T1DM) in children. The significant reductions observed in fasting blood glucose, postprandial blood glucose, and glycosylated hemoglobin levels, along with the reduced need for daily insulin dosage, highlight the potential of this combination therapy in improving glycemic control. Importantly, these improvements could contribute positively to the physical fitness and participation in games and physical activities of children with T1DM, which are crucial aspects of their overall development and quality of life.

However, the increased incidence of gastrointestinal adverse reactions associated with this therapy underscores the necessity for vigilant monitoring and patient-specific considerations in clinical practice. These findings advocate for a balanced approach in the treatment of pediatric T1DM, weighing the benefits of enhanced glycemic control and potential improvements in physical activity participation against the risks of adverse effects. In metformin and insulin combination therapy emerges as a promising option for improving the management of T1DM in children, with potential positive implications for their physical activity engagement. Further research, especially longitudinal studies focusing on long-term outcomes related to physical fitness and game participation, is needed to fully establish the role of this therapy in the holistic care of children with T1DM.

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