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Metformin and Insulin: An Effective Therapeutic Combination for Overweight and Obese Type 1 Diabetes Patients?

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ABSTRACT

Type 1 Diabetes (T1D) is a chronic autoimmune disease characterized by insulin deficiency due to the destruction of pancreatic beta cells. Patients with T1D who are overweight or obese face additional challenges in management due to insulin resistance, making their condition more complex to treat. This systematic review evaluates the efficacy of adding metformin to insulin monotherapy in improving glycemic control and body mass index (BMI). This study retrieved data from databases including PubMed, ScienceDirect, Scopus, and ProQuest, adhering to PRISMA guidelines. After screening 402 studies, 4 randomized controlled trials met the inclusion criteria. These trials compared the impact of metformin with placebo or insulin monotherapy on HbA1c, fasting plasma glucose (FPG), and BMI. The results showed that metformin adjunct therapy provided limited impact on HbA1c and FPG levels while demonstrating significant improvements in BMI. In conclusion, adding metformin to insulin therapy can aid in improving BMI in overweight or obese T1D patients, though its effects on glycemic control remain inconclusive. Further high-quality studies are recommended to validate these findings.

Keywords: type 1 diabetes; obesity; overweight; insulin; metformin; glycemic; BMI.

INTRODUCTION

Type 1 Diabetes (T1D) is a chronic autoimmune disease characterized by insulin deficiency due to the destruction of pancreatic beta cells. This condition leads to hyperglycemia and requires lifelong insulin therapy for glycemic control [1]. T1D predominantly affects children and young adults and is often associated with complications such as diabetic ketoacidosis and long-term vascular diseases [2].

In Indonesia, the prevalence of T1D has been rising, with over 41,000 diagnosed cases reported in 2022, making it the highest in the ASEAN region. The management of T1D becomes more complex when accompanied by overweight or obesity, conditions that exacerbate insulin resistance and impair peripheral glucose uptake [3]. Obesity also disrupts the adipo-insular axis, altering adipokine secretion (e.g., leptin, adiponectin) and increasing free fatty acids in plasma, which further impairs beta-cell function and increases glucose production in the liver [4].

Metformin, a biguanide widely used in the treatment of Type 2 Diabetes (T2D), has been proposed as an adjunct therapy for T1D, particularly in patients with overweight or obesity [1]. Metformin works by reducing hepatic glucose production, enhancing peripheral insulin sensitivity, and promoting modest weight loss [5][6][7]. Additionally, its pleiotropic effects, such as improving lipid profiles and reducing inflammation, make it a promising candidate for addressing the metabolic challenges of T1D with obesity [8][9][10]. Despite these theoretical benefits, clinical evidence on the efficacy of metformin as an adjunct to insulin therapy in T1D remains inconclusive. Previous studies have shown mixed results, particularly regarding its effects on glycemic control (HbA1c, FPG) and body mass index (BMI).

METHODS

This study adhered to the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analyses) guidelines and included only randomized controlled trials (RCTs).

Databases including PubMed, ScienceDirect, Scopus, and ProQuest were searched comprehensively using relevant keywords such as "type 1 diabetes," "metformin," "insulin," "obesity," and "overweight." The search was conducted without time restrictions to maximize the inclusion of relevant studies.

The inclusion criteria for this review were studies involving T1D patients with overweight or obesity, RCTs evaluating the effect of adding metformin to insulin therapy, and outcomes measuring HbA1c, FPG, and/or BMI. Exclusion criteria included non-RCT studies, studies without sufficient outcome data, or the sample of the study receiving any other therapy besides the metformin and insulin combination.

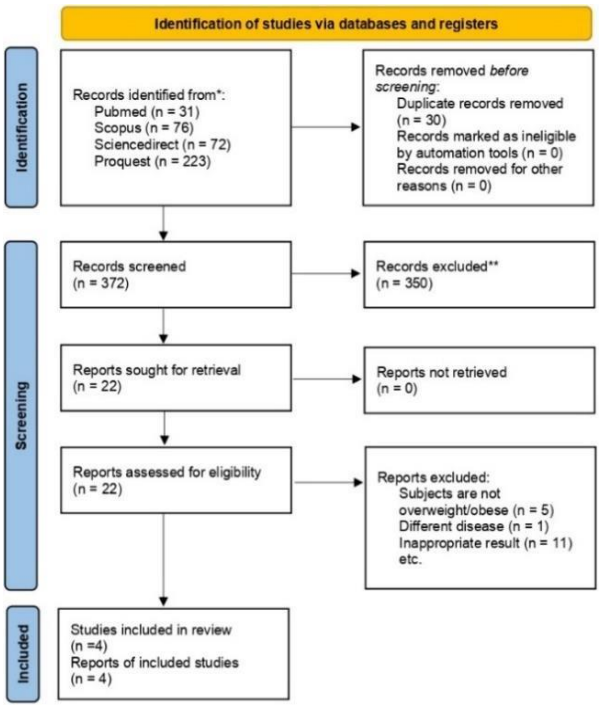

FIGURE 1: Study selection according to PRISMA flow chart.

The search results were screened for duplicates, titles, and abstracts. Full-text articles were assessed for eligibility based on the inclusion criteria. Data extraction included study characteristics, participant demographics, intervention details, and outcomes. The methodological quality of the included studies was evaluated using the Risk of Bias 2 (RoB 2) tool. Each study will be categorized into low risk, some concerns, or high risk of bias.

RESULTS

Results of Search and Screening

A total of 402 records were identified through database searches. After removing duplicates, 350 unique studies were screened based on titles and abstracts. Of these, 22 articles were assessed for eligibility through full-text review, and four RCTs met the inclusion criteria for this systematic review. The PRISMA flow chart summarizing the study selection process is presented in Figure 1.

Characteristics of the Included Studies

The detailed characteristics of the included articles are shown in Table 1 and Table 2. All four articles were RCTs. A total of 294 patients were included, with 171 patients in the intervention group and 123 patients in the control group. The age distribution showed that most of the patients were in the young adult age group. All studies included patients with overweight or obese BMI according to the WHO classification. The duration of the studies varied: studies by Burchardt et al. and Zawada et al. were conducted over 6 months, while a study by Nwosu et al. lasted 9 months, and a study by Lund et al. was conducted over 12 months.

All studies diagnosed T1D through specific antibody testing and clinical symptoms, with all studies including patients who had been diagnosed with T1D for over one year. In the intervention group, all studies administered metformin with an average daily dosage of over 1000 mg, while in the control group, some participants received a placebo and others were given insulin only. The outcome measures collected from each study included blood glucose indicators such as HbA1c and GDP, as well as BMI, both before and after the intervention.

The Bias Risk of the Included Studies

Table 3 provides a detailed assessment of the risk of bias in the studies. Three of them were categorized as low risk and one study categorized as some concerns according to Risk of Bias 2.

DISCUSSION

The results of this systematic review reveal varied effects of metformin on clinical parameters in overweight or obese T1D patients compared to control groups. Across all studies, reductions in mean HbA1c levels were observed following intervention, although the magnitude of reduction varied between studies. Regarding FPG, three studies by Burchardt et al., Nwosu et al., and Zawada et al. demonstrated a decrease in FPG, while one study reported a slight increase. For BMI, all studies reported different outcomes between the groups, highlighting the heterogeneity in response to metformin.

Several factors may influence BMI, aside from blood glucose levels, including dietary habits, physical activity, and pre-intervention medical conditions [11]. Hypoglycemia episodes, for instance, can lead to compensatory food and drink intake, affecting not only HbA1c but also BMI. Moreover, Nwosu et al. included younger populations (adolescents), which might have influenced adherence rates (65%) and contributed to less pronounced effects on BMI.

The variability in HbA1c and GDP outcomes observed across studies may also stem from factors such as patient age and baseline health conditions. For example, Beysel et al. reported that metformin reduced blood glucose levels and daily insulin requirements but did not achieve significant reductions in HbA1c levels [12].

Similarly, Jacobsen et al. and Lund et al. found that metformin primarily reduced daily insulin needs without improving glycemic control parameters [13][14]. Prolonged interventions of up to three years also failed to demonstrate significant HbA1c reductions [15].

TABLE 1: Study design and baseline characteristics of the included studies.

Study and publication year	Study design	Sample size		Age*		Duration of therapy	Trial Arm		Final dose of metformin per day
		I	C	I	C		I	C	
Nwosu et al., 2015	RCT	15	13	15	14.5	9 months	Met+Ins	Ins+PL	1000 mg
Lund et al., 2008	RCT	49	51	46.1	44.9	12 months	Met+Ins	Ins+PL	2000 mg
Zawada et al., 2018	RCT	74	40	32	27.5	6 months	Met+Ins	Ins only	2550 mg
Burchardt et al., 2013	RCT	35	33	35.3	30.5	6 months	Met+Ins	Ins only	2550 mg

*Age is shown as the median (range).
#RCT: randomized controlled trial; I: intervention group; C: control group; Met: metformin; Ins: Insulin; PL: Placebo.

TABLE 2: Participant characteristics before and after treatment.

Study and publication year	Group	HbA1c (%)		FPG (mg/dL)		BMI (kg/m^2)		DID (unit/kg)	
		Baseline	EOT	*Baseline*	EOT	*Baseline*	EOT	*Baseline*	EOT
Nwosu et al., 2015	Intervention	9.3	8.85	193.1	189.4	27.7	28.8	1.1	1.73
	Control	8.7	7.98	193.9	170.5	28.0	28.6	1.44	1.42
Lund et al., 2008	Intervention	9.34	9.25	198.35	199.07	26.11	25.61*	0.74	0.71
	Control	9.35	9.12	239.6	223.57	25.78	25.85	0.74	0.77
Zawada et al., 2018	Intervention	8.6	8.0*	167.45	127.81*	28.8	28.4*	0.5	0.46
	Control	8.2	8.4	163.4	174.2	27.5	28.1	0.6	0.58
Burchardt et al., 2013	Intervention	9.0	7.7	182.2	126.4*	29.5	28.9	NR	NR
	Control	8.3	8.1	170.8	207.3	27.1	27.3	NR	NR

*Statistically significant ($p < 0,005$).
#FPG: fasting plasma glucose; BMI: body mass index; DID: daily insulin dose; EOT: end of treatment; NR: not reported.

TABLE 3: Risk of bias assessment of individual studies.

Study and publication year	Domain 1	Domain 2	Domain 3	Domain 4	Domain 5	Overall
Nwosu et al., 2015	Low	Low	Low	Low	Low	Low
Lund et al., 2008	Low	Low	Low	Low	Low	Low
Zawada et al., 2018	Some concerns	Low	Low	Low	Low	Some concerns
Burchardt et al., 2013	Low	Low	Low	Low	Low	Low

#Domain 1: Bias arising from the randomization process; Domain 2: Bias due to deviations from intended interventions; Domain 3: Bias due to missing outcome data; Domain 4: Bias in measurement of the outcome; Domain 5: Bias in selection of the reported result.

Contrastingly, metformin's efficacy in BMI reduction appears more consistent. Liu & Yang found no significant BMI reductions in adolescents with T1D [16], while Al Khalifah et al. reported a reduction of 1.46 kg/m^2 in children with T1D following metformin therapy [17]. Beyond glycemic and BMI outcomes, metformin also offers metabolic benefits, including improvements in lipid profiles [18].

This review underscores the variability in metformin's effects, influenced by factors such as dosage, duration, and patient characteristics. While metformin shows promise as adjunctive therapy in overweight or obese T1D patients, further studies with standardized protocols and larger samples are needed to confirm its long-term efficacy and safety.

LIMITATIONS

However, this study has several limitations. The number of articles meeting the inclusion criteria was limited, reducing the generalizability of the findings to all T1D cases. Second, the inclusion of a study with a "some concerns" risk of bias necessitates careful interpretation of the results. Inconsistencies in metformin and insulin dosages, as well as variations in the types of insulin used between intervention and control groups, pose additional limitations. Lastly, this review did not include other critical metabolic parameters, such as lipid profiles, which are important for managing T1D patients.

Future studies should aim to address these limitations by including a larger number of trials with standardized dosage regimens and extending the evaluation to additional metabolic parameters, such as lipid profiles. Furthermore, long-term investigations into the cardiovascular and renal effects of metformin in overweight and obese T1D populations are warranted to provide a more comprehensive understanding of its therapeutic potential.

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