Comparison of metformin, dapagliflozin, and their combination in the management of Type 2 diabetes mellitus: A review

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ABSTRACT

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder with a high global prevalence, including in Indonesia. Metformin is the most commonly used first-line therapy. However, disease progression often necessitates combination therapy. Dapagliflozin, an SGLT2 inhibitor, has been shown to reduce blood glucose levels and body weight. This review aims to compare the effectiveness, safety, and cost-effectiveness of metformin, dapagliflozin, and their combination in patients with T2DM. A literature search was conducted through PubMed, NCBI, and Google Scholar using relevant keywords. Inclusion criteria included publications from 2015 to 2025 that compared metformin, dapagliflozin, and their combination. Five studies meeting the criteria were analyzed to assess therapeutic effectiveness, safety, and cost-effectiveness. Combination therapy with dapagliflozin and metformin resulted in significantly greater reductions in HbA1c and body weight, as well as improvements in metabolic parameters, compared with monotherapy. The combination demonstrated a favorable safety profile, with a mild increase in urinary tract and genital infections that were generally well tolerated. Pharmacoeconomic analyses indicated that early initiation of combination therapy was more cost-effective in the long term than a stepwise approach. Dapagliflozin–metformin combination therapy is more effective and cost-efficient than monotherapy for managing T2DM, with an acceptable safety profile. This regimen may be considered as an alternative for patients who do not achieve glycaemic targets with monotherapy.

Keywords: diabetes mellitus, type 2; metformin, dapagliflozin, Indonesia

Introduction

Diabetes mellitus (DM) is a chronic metabolic disorder that occurs when insulin function is impaired, resulting in suboptimal regulation of blood glucose levels and, consequently, hyperglycaemia.[1] The most common type of DM worldwide is type 2 diabetes mellitus (T2DM), accounting for more than 95% of all cases. According to the World Health Organization (2025), approximately 830 million people worldwide live with DM, most of them in low- and middle-income

countries. More than half of people with DM still lack adequate access to treatment. In Indonesia, the prevalence of DM increased from 6.9% in 2013 to 10.9% in 2018, based on the National Basic Health Research (Riskesdas) report.[2] This increase is influenced by several factors, including age, lifestyle, history of certain diseases, genetic predisposition to other health conditions, and the use of specific medications.[3,4]

Management of T2DM includes various pharmacological therapies, including metformin, sulfonylureas, thiazolidinediones, DPP-4 inhibitors, SGLT2 inhibitors, GLP-1 receptor agonists, and insulin.[5,6] Drug selection is tailored to the patient's condition and glycaemic control targets.[7] Metformin remains the recommended first-line therapy for glycaemic management in patients with T2DM and has been proven to significantly reduce glycated haemoglobin (HbA1c) levels.[8–10] However, as the disease progresses, metformin monotherapy is often insufficient to maintain optimal blood glucose control. Standard T2DM management typically begins with lifestyle modifications alongside metformin therapy.

Dapagliflozin, a member of the sodium-glucose cotransporter 2 (SGLT2) inhibitor class, is a newer oral antidiabetic agent that has demonstrated the ability to lower both HbA1c and body weight in patients with T2DM, whether as monotherapy or in combination with other antidiabetic drugs.[11,12] Dapagliflozin works by inhibiting glucose reabsorption in the proximal renal tubules, thereby increasing urinary glucose excretion and lowering blood glucose levels. It is recommended for the management of T2DM due to its sustained effects in reducing blood glucose and HbA1c.[13]

Metformin, a biguanide, exerts its effects through both AMP-activated protein kinase (AMPK)-dependent and AMPK-independent mechanisms, inhibiting key enzymes involved in gluconeogenesis and lipogenesis. This review aims to evaluate and compare the effectiveness of dapagliflozin and metformin, both as monotherapy and in combination therapy, in patients with T2DM.

Method

This review used an electronic literature search across PubMed, NCBI, and Google Scholar databases to identify studies comparing metformin, dapagliflozin, and their combination in the management of T2DM. The search was limited to articles published between January 2015 and March 2025 using the keywords *"metformin, dapagliflozin, combination therapy,* and *type 2 diabetes mellitus"*. Studies were included if they were published in peer-reviewed journals, assessed outcomes such as glycaemic control (HbA1c), metabolic parameters, safety, or cost-effectiveness, and were available in full text. Exclusion criteria included studies involving paediatric populations or type 1 diabetes mellitus, case reports, editorials, letters to the editor, articles with insufficient data, and duplicate publications. Five studies met all criteria and were included in the qualitative synthesis. The selection process followed PRISMA guidelines and is summarized in the flow diagram (Figure 1).

Results

Based on the inclusion and exclusion criteria outlined in the methods, 356 articles were identified, from which five articles were selected that compared the use of metformin, dapagliflozin, and their combination in patients with T2DM. These articles were analyzed to evaluate the effectiveness, safety, and cost-effectiveness of each therapeutic regimen. A summary of the findings from these five studies is presented in Table 1.

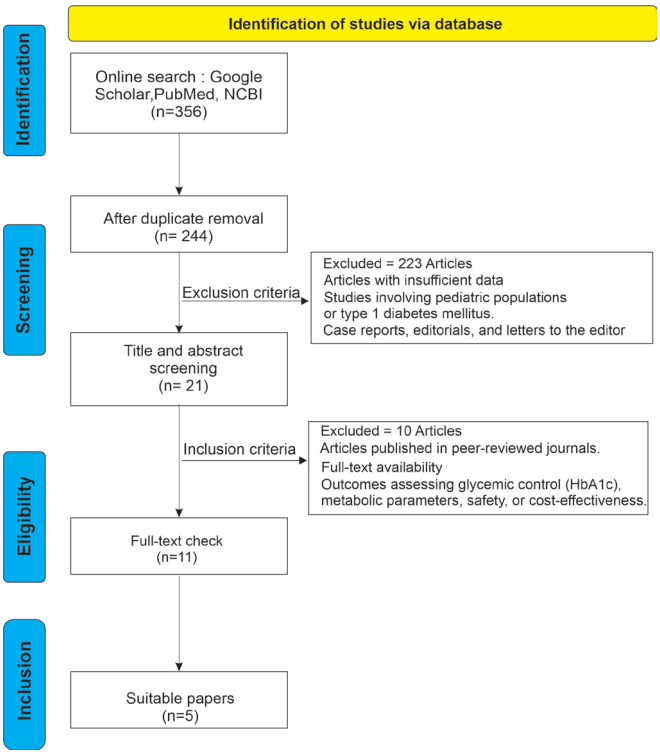

Figure 1. PRISMA Flow Diagram of Study Selection

Table 1. Comparison of metformin and dapagliflozin use in type 2 diabetes mellitus patients

Reference	Method	Result
Efficacy (including safety)		
[14]	This study included 248 patients admitted to Jiangxi Provincial People's Hospital from January 1, 2017, to December 31, 2019, with a diagnosis of metabolic syndrome. Participants were randomly assigned into three groups: dapagliflozin, metformin, and dapagliflozin plus metformin.	The combination of dapagliflozin and metformin produced greater improvements across all aspects of metabolic syndrome compared to either drug used alone.
[12]	This open prospective study was conducted over a period of six months at a tertiary teaching hospital in Jammu, involving 60 obese women with new-onset T2DM who met the inclusion and exclusion criteria.	The combination of dapagliflozin with metformin showed higher effectiveness than metformin monotherapy in achieving optimal glycaemic control.
[15]	A systematic review of randomized controlled trials was conducted, and the Cochrane risk of bias tool was used for quality assessment. The Patients, Interventions, Comparisons, and Outcomes (PICO) technique was used to select relevant articles to meet the objectives.	Combination therapy with metformin and SGLT2 inhibitors was more effective in lowering HbA1c and body weight than metformin monotherapy alone. Among the three SGLT2 inhibitors, dapagliflozin, canagliflozin, and empagliflozin, weight loss efficacy was not significantly different..
[16]	The MEDLINE and Embase databases were searched for controlled studies including dapagliflozin sodium, randomized controlled trials (RCTs), metformin, and efficacy. The search was limited to English language, human studies, randomized controlled trials, and clinical trials (phase 3 and phase 4).	The combined use of dapagliflozin and metformin has demonstrated both safety and efficacy in treating T2DM, with only minor adverse effects.
Cost-effectiveness		
[17]	Data between January 1, 2013 and December 31, 2016 were analyzed to determine the time required to add an SGLT2 inhibitor in patients starting metformin monotherapy.	Initiating treatment with a combination of dapagliflozin and metformin as first-line therapy may offer a more cost-effective strategy for managing T2DM patients in Australia compared to starting with metformin alone and subsequently adding dapagliflozin.

Discussion

Diabetes mellitus (DM) is a chronic metabolic disease characterized by elevated blood glucose levels due to insufficient insulin production (type 1 DM) or resistance to insulin's effects (T2DM).[18,19] Diagnosis of DM involves fasting plasma glucose (FPG), glycated haemoglobin (HbA1c), and oral glucose tolerance tests (OGTT).[20,21] Management of T2DM typically begins with lifestyle modification and metformin as first-line therapy due to its effectiveness in reducing HbA1c, low risk of hypoglycaemia, and relatively low cost.[22] However, if glycaemic targets are not achieved, combination therapy with other oral antidiabetic drugs (OADs) is often required to control hyperglycaemia and prevent long-term complications. One of the newer drug classes used as an add-on therapy is sodium–glucose cotransporter 2 (SGLT2) inhibitors, which work by inhibiting glucose

reabsorption in the kidney and increasing urinary glucose excretion. Dapagliflozin, an approved SGLT2 inhibitor, can be used as monotherapy or in combination with metformin. Recent clinical guidelines, including the American Diabetes Association (ADA) 2025 Standards of Care, European Association for the Study of Diabetes (EASD) consensus reports, and Indonesian Society of Endocrinology (PERKENI) guidelines, recommend metformin as initial pharmacotherapy, with SGLT2 inhibitors prioritized as add-on agents, particularly for patients with cardiovascular disease, heart failure, or chronic kidney disease due to their proven cardiometabolic benefits. This review aims to evaluate the effectiveness and safety of dapagliflozin–metformin combination therapy in patients with T2DM.[23,24]

Both dapagliflozin and metformin are widely used oral antidiabetic agents for T2DM. Evidence from multiple studies demonstrates the superior efficacy of their combination therapy compared with either drug alone. Cheng et al. (2021) reported significant improvements in metabolic syndrome components, including reductions in body weight, BMI, waist circumference, fasting blood glucose, insulin resistance (HOMA-IR), hs-CRP, and lipid profiles with the combination versus monotherapy. Similarly, Singh et al. (2024) found that obese women over 40 years with newly diagnosed T2DM experienced greater HbA1c reductions (>10%) compared to metformin alone (4.46%, $p < 0.001$), with effects sustained through week 12. A systematic review by Molugulu et al. (2017) further confirmed that combination therapy with metformin and SGLT2 inhibitors, including dapagliflozin, significantly lowered HbA1c and body weight across all included RCTs ($p < 0.05$).

Safety is an important consideration in diabetes therapy to prevent long-term adverse effects. According to Alkhanferi et al. (2022), dapagliflozin–metformin combination therapy demonstrated a favorable safety profile. The combination did not significantly increase hypoglycaemia or electrolyte disturbances compared to metformin alone. However, a higher incidence of urinary tract infections (UTIs) and genital infections was observed in patients receiving dapagliflozin, although these were generally mild and did not lead to treatment discontinuation. This suggests that the adverse effects of dapagliflozin are generally tolerable, especially when its clinical benefits outweigh the potential risks.

Cost-effectiveness analysis compares the relative costs and outcomes of health interventions, and Chin et al. (2019) reported that dapagliflozin–metformin as first-line therapy was more cost-effective than sequential addition of dapagliflozin to metformin monotherapy. Early combination therapy reduced hospitalization for heart failure by 5.5%, cardiovascular mortality by 57.6%, and all-cause mortality by 29.6%, adding 1.9 quality-adjusted life years (QALYs) per patient with an incremental cost-effectiveness ratio (ICER) of AUD 12,477 per QALY, within Australia's cost-effectiveness threshold. Overall, evidence consistently shows that the combination provides superior glycaemic control, greater weight reduction, and improved metabolic outcomes compared with monotherapy, with a favorable safety profile marked by only a slight increase in mild UTI risk, supporting its role as a promising therapeutic option for patients with T2DM inadequately controlled on monotherap

Most included studies originated in Asia or Australia, limiting their direct applicability to African populations, where healthcare infrastructure, diagnostic capacity, and medication access differ significantly. To improve feasibility in African settings, several practical strategies can be adopted. First, governments and health agencies could negotiate tiered pricing or pooled procurement agreements with pharmaceutical companies to lower costs and expand access to SGLT2 inhibitors. Second, once available, generic formulations should be prioritized to reduce treatment costs. Third, task-shifting diabetes care to trained primary care providers and community health workers can help address shortages of endocrinologists and specialists. Fourth, integrating diabetes management into existing noncommunicable disease programmes such as hypertension or HIV care platforms can leverage existing infrastructure and reduce costs. Finally, local implementation research should be conducted to assess real-world effectiveness, safety, and cost-effectiveness, ensuring that recommendations are adapted to each country's healthcare capacity and economic constraints.

It is also important to consider the accessibility of dapagliflozin. Although the drug has been included in the WHO Essential Medicines List, its availability and affordability remain limited in many low- and middle-income countries. This creates a significant barrier to its widespread use in the populations that may benefit the most. Furthermore, while urinary tract and genital infections associated with dapagliflozin are generally mild and manageable in high-resource settings, they may pose a greater health burden in resource-poor countries where access to timely diagnosis and treatment is limited. Evidence from a study involving 2,990 patients with T2DM in China showed that the incidence of urinary

tract infection was only 2.1–2.3%, and genital infection 1.5%, confirming that these adverse events are relatively uncommon and generally well tolerated.[25] However, these findings largely reflect data from higher-resource settings, and the lack of large-scale safety and cost-effectiveness studies in low-income regions limits their generalisability. Future research should incorporate local drug pricing, healthcare infrastructure, and resource availability to ensure therapeutic recommendations are evidence-based and context-specific.

Conclusion

Based on the review of five studies, the combination of dapagliflozin and metformin demonstrated superior effectiveness in reducing HbA1c levels, body weight, and improving metabolic parameters compared to metformin or dapagliflozin monotherapy. In terms of safety, the combination was generally well tolerated, although a slight increase in the incidence of non-severe urinary tract and genital infections was observed. These findings are further supported by evidence of cost efficiency, indicating that combination therapy is more cost-effective in the long term compared to a stepwise approach. Therefore, dapagliflozin–metformin combination therapy may be considered as an alternative for patients with T2DM who have not achieved therapeutic targets with monotherapy. Nevertheless, its use should be tailored to each patient's clinical condition, taking into account the therapy's risks, benefits, and accessibility.

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Ethical approvals: Not applicable.

Data availability: All data supporting the findings of this review are derived from previously published studies, which are properly cited in the reference list.

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