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# EFFICACY AND SAFETY OF EMPAGLIFLOZIN COMBINED WITH METFORMIN (JARDIANCE DUO) IN GLYCEMIC CONTROL OF PATIENTS WITH TYPE 2 DIABETES MELLITUS

# EFICÁCIA E SEGURANÇA DO USO DE EMPAGLIFLOZINA ASSOCIADA À METFORMINA (JARDIANCE DUO) NO CONTROLE GLICÊMICO DE PACIENTES COM DIABETES MELLITUS TIPO 2

# EFICACIA Y SEGURIDAD DEL USO DE EMPAGLIFLOZINA COMBINADA CON METFORMINA (JARDIANCE DUO) EN EL CONTROL GLUCÉMICO DE PACIENTES CON DIABETES MELLITUS TIPO 2

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**Valéria Goulart Viana[1], Rafaella Abrantes e Silva[2], Guilherme Diniz Marcelino[3], Hanna Fauzi Abdul Rahim[4], Bruna Gabriela Frizzo Alexandre[5], Nathalia Santos Gonçalves[6], Victor Talles de Melo Fontenelle[7], Lidiana Fortunato Correa[8], Carlos Arthur Marinho da Silva Beltrão[9], Edermeson Roque Malheiro Brandão[10], Júlia Maria Soares da Silva[11], Lia Amaral de Sousa[12], José Severino Campos Neto[13], Flávia Viana Henriques Lôbo Costa[14], Maurício Cavalcante Paixão[15], Marcella de Fátima Lomeu Marinho[16], Júlia Maia Vilela Barros[17], Alexandre dos Santos Vasques[18], Karina Cristina dos Santos[19], Pedro Henrique Pessoa Português de Souza[20], Brenda Emanuelly de Campos Ferreira[21], Nelson Freire Silva Filho[22]**

[1] Medical Doctor. Faculdade de Medicina de Itajubá. E-mail: dravaleriagoulart@yahoo.com.br
[2] Medical Doctor. Centro Universitário Facisa (UNIFACISA). E-mail: rafaella_abrantes@hotmail.com
[3] Medical Doctor. Universidad María Auxiliadora (UMAX). E-mail: guidiiniz12@gmail.com
[4] Medical Doctor. Universidade São Judas Tadeu. E-mail: hanna.rahim@outlook.com
[5] Medical Doctor. Universidade Luterana do Brasil. E-mail: brunafrizzoa@gmail.com
[6] Medical Doctor. Faculdade Meridional – IMED (Atual Atitus Educação).
E-mail: nathisgoncalves@outlook.com
[7] Medical Doctor. Universidade Potiguar. E-mail: victorfontenelle@hotmail.com
[8] Medical Doctor. Universidade do Grande Rio Professor José de Souza Herdy (UNIGRANRIO).
E-mail: lidianafortunatocorrea@gmail.com
[9] Medical Doctor. Universidade do Estado do Amazonas (UEA). E-mail: carlosarthurbeltrao@gmail.com
[10] Medical Doctor. Universidade Estadual do Sudoeste da Bahia. E-mail: edermesonbrandao@gmail.com
[11] Medical Doctor. Centro Universitário Uninovafapi (UNINOVAFAPI). E-mail: juliamssilva01@gmail.com
[12] Medical Doctor. Universidade Federal do Pará (UFPA). E-mail: lia.amaralsousa@gmail.com
[13] Specialist in Family and Community Medicine. Universidade Federal de Santa Catarina.
E-mail: netocampos_1@yahoo.com.br
[14] Medical Doctor. Universidade Federal do Cariri (UFCA). E-mail: flaviavh@gmail.com
[15] Medical Doctor. Universidade do Estado do Amazonas. E-mail: mpaixao210720@gmail.com
[16] Medical Residency in Internal Medicine. Hospital Rede Casa de Portugal.
E-mail: marcellamarinho1979@gmail.com
[17] Medical Doctor. Centro Universitário Maurício de Nassau (UNINASSAU). E-mail: juliamvbarros@gmail.com
[18] Medical Doctor. Universidade Federal de Rondonópolis. E-mail: vasquessalexandre@gmail.com
[19] Dr. Universidade Federal do Cariri (UFCA). Universidade Federal de Minas Gerais (UFMG).
E-mail: karinacristinas1028@gmail.com
[20] Medical Doctor. Pontifícia Universidade Católica de Goiás (PUC-GO). E-mail: phportugues@hotmail.com
[21] Medical Doctor. Universidade Federal de São Carlos (UFSCar). E-mail: becf2001@gmail.com
[22] Medical Doctor. Universidade Federal de Goiás (UFG). E-mail: nelsonfreire@egresso.ufg.br

**ABSTRACT**
Type 2 diabetes mellitus (T2DM) is a chronic metabolic disease characterized by insulin resistance and progressive β-cell dysfunction, resulting in persistent hyperglycemia. Metformin, the first-line drug for T2DM treatment, is often insufficient to maintain long-term glycemic control, requiring combination therapy with other antihyperglycemic agents. Among the new therapeutic options, empagliflozin, a selective sodium-glucose cotransporter 2 (SGLT2) inhibitor, stands out for its additional benefits on body weight, blood pressure, and cardiovascular and renal function. Therefore, this study aimed to analyze scientific evidence published over the last ten years regarding the efficacy and safety of the empagliflozin/metformin combination (Jardiance Duo) in glycemic control of patients with T2DM. This is an integrative literature review conducted in the PubMed, SciELO, ScienceDirect, and Scopus databases, including articles published between 2015 and 2025. A total of 11 studies met the eligibility criteria. The findings showed that the combined therapy promotes significant reductions in glycated hemoglobin (HbA1c), improved glycemic control, and additional metabolic benefits, with a favorable safety profile and low incidence of severe adverse events. In conclusion, the empagliflozin/metformin combination is effective, safe, and cost-effective, representing a promising therapeutic strategy for the management of type 2 diabetes mellitus and aligned with current national and international clinical guidelines.

**Keywords:** Type 2 Diabetes Mellitus. Empagliflozin. Metformin. Combination Therapy. Integrative Review.

**RESUMO**
O diabetes mellitus tipo 2 (DMT2) é uma doença metabólica crônica caracterizada pela resistência à insulina e pela disfunção progressiva das células β pancreáticas, resultando em hiperglicemia persistente. A metformina, fármaco de primeira escolha no tratamento do DMT2, muitas vezes se mostra insuficiente para manter o controle glicêmico adequado a longo prazo, exigindo a associação com outros agentes hipoglicemiantes. Entre as novas opções terapêuticas, destaca-se a empagliflozina, inibidor seletivo do cotransportador sódio-glicose tipo 2 (SGLT2), que apresenta benefícios adicionais sobre o peso corporal, a pressão arterial e a função cardiovascular e renal. Diante disso, este estudo teve como objetivo analisar as evidências científicas publicadas nos últimos dez anos sobre a eficácia e segurança da associação empagliflozina/metformina (Jardiance Duo) no controle glicêmico de pacientes com DMT2. Trata-se de uma revisão integrativa da literatura, realizada nas bases PubMed, SciELO, ScienceDirect e Scopus, incluindo artigos publicados entre 2015 e 2025. Foram selecionados 11 estudos que atenderam aos critérios de elegibilidade. Os resultados evidenciaram que a terapia combinada promove reduções significativas da hemoglobina glicada (HbA1c), melhora do controle glicêmico e benefícios metabólicos adicionais, com perfil de segurança favorável e baixa incidência de eventos adversos graves. Conclui-se que a associação empagliflozina/metformina é eficaz, segura e custo-efetiva, configurando-se como uma estratégia terapêutica promissora para o manejo do diabetes mellitus tipo 2 e alinhada às diretrizes clínicas nacionais e internacionais.

**Palavras-chave:** Diabetes Mellitus Tipo 2. Empagliflozina. Metformina. Terapia Combinada. Revisão Integrativa.

**RESUMEN**
La diabetes mellitus tipo 2 (DM2) es una enfermedad metabólica crónica caracterizada por resistencia a la insulina y disfunción progresiva de las células β pancreáticas, lo que resulta en hiperglucemia persistente. La metformina, fármaco de primera línea en el tratamiento de la DM2, a menudo resulta insuficiente para mantener un control glucémico adecuado a largo plazo, requiriendo la combinación con otros hipoglucemiantes. Entre las nuevas opciones terapéuticas, destaca la empagliflozina, un inhibidor selectivo del cotransportador de sodio-

glucosa tipo 2 (SGLT2), que ofrece beneficios adicionales sobre el peso corporal, la presión arterial y la función cardiovascular y renal. Por lo tanto, este estudio tuvo como objetivo analizar la evidencia científica publicada en los últimos diez años sobre la eficacia y seguridad de la combinación empagliflozina/metformina (Jardiance Duo) en el control glucémico de pacientes con DM2. Se trata de una revisión bibliográfica integradora, realizada en las bases de datos PubMed, SciELO, ScienceDirect y Scopus, que incluye artículos publicados entre 2015 y 2025. Se seleccionaron once estudios que cumplieron con los criterios de elegibilidad. Los resultados mostraron que la terapia combinada promueve reducciones significativas de la hemoglobina glucosilada (HbA1c), mejora el control glucémico y beneficios metabólicos adicionales, con un perfil de seguridad favorable y una baja incidencia de eventos adversos graves. Se concluye que la combinación empagliflozina/metformina es eficaz, segura y rentable, lo que representa una estrategia terapéutica prometedora para el manejo de la diabetes mellitus tipo 2 y se ajusta a las guías clínicas nacionales e internacionales.

**Palabras clave:** Diabetes Mellitus Tipo 2. Empagliflozina. Metformina. Terapia Combinada. Revisión Integradora.

## 1 INTRODUCTION

Type 2 Diabetes Mellitus (T2DM) is a chronic metabolic disease characterized by insulin resistance and progressive dysfunction of pancreatic β cells, resulting in persistent hyperglycemia. Its global increase has become a serious public health problem, associated with micro and macrovascular complications, increased mortality, and reduced quality of life (INTERNATIONAL DIABETES FEDERATION, 2023). In Brazil, the prevalence of T2DM has been growing continuously in recent decades, driven by factors such as obesity, sedentary lifestyle, and population aging (SOCIEDADE BRASILEIRA DE DIABETES, 2023). In this scenario, effective glycemic control is one of the main therapeutic objectives in the management of the disease, aiming to reduce complications and improve the prognosis of patients.

Metformin, belonging to the class of biguanides, is considered the drug of choice in the treatment of T2DM, as it reduces hepatic glucose production and improves peripheral insulin sensitivity, in addition to having a low risk of hypoglycemia and favorable effects on body weight (GOLDMAN et al., 2018). However, in many patients, metformin monotherapy becomes insufficient to maintain adequate glycemic control in the long term, requiring the association of other hypoglycemic agents with complementary mechanisms of action (HADJADJ et al., 2016). This therapeutic need has driven the development of pharmacological combinations capable of acting synergistically in the metabolic control of diabetes.

Empagliflozin, a selective inhibitor of the sodium-glucose cotransporter type 2 (SGLT2), works by promoting urinary glucose excretion, which contributes to the reduction of blood glucose, body weight, and blood pressure (ZHONG et al., 2016). In addition, it has cardiovascular and renal benefits proven in large clinical trials, which has significantly expanded its role in the management of T2DM (JARDIANCE STUDY GROUP, 2020). The empagliflozin/metformin combination (commercially called Jardiance Duo) combines distinct and complementary mechanisms of action, providing greater efficacy in reducing glycated hemoglobin (HbA1c), without a relevant increase in the risk of hypoglycemia (WAZIR; REHMAN, 2022).

Clinical studies and systematic reviews have shown the efficacy and safety of the empagliflozin/metformin combination in patients with T2DM. Hadjadj et al. (2016) demonstrated significant reductions in HbA1c and body weight compared to monotherapy. Reviews by Kedia et al. (2016) and Goldman et al. (2018) reinforce that the combination has

a favorable safety profile and additional improvement in glycemic control, while recent studies, such as the one by Park et al. (2024), confirm maintenance of glycemic and metabolic effects in prolonged therapies. However, despite the growing number of publications, the literature still lacks an **integrative and critical synthesis** that consolidates the evidence on the efficacy and safety of this pharmacological association in different clinical contexts and populations.

Considering the high prevalence of type 2 diabetes mellitus and the therapeutic limitations of hypoglycemic agents alone, understanding the clinical effects of the empagliflozin/metformin combination is essential to support more effective clinical practices, reduce metabolic complications, and optimize the therapeutic management of patients. In this context, the present study aims to **critically analyze the available scientific evidence on the efficacy and safety of the combined therapy of empagliflozin and metformin in the glycemic control of individuals with type 2 diabetes mellitus**, through an integrative review of the literature. The research seeks to answer the following guiding question: *what is the scientific evidence published in the last ten years that addresses the efficacy and safety of empagliflozin associated with metformin in the treatment of type 2 diabetes mellitus?*

## 2 METHODOLOGY

The present research is an **integrative literature review**, designed with the purpose of identifying, gathering, critically evaluating and synthesizing the available scientific evidence about the **efficacy and safety of the empagliflozin/metformin association (Jardiance Duo)** in the glycemic control of patients with **type 2 Diabetes Mellitus (DMT2)**. This type of review allows the integration of results from experimental and non-experimental studies, providing a comprehensive understanding of the phenomenon investigated (SOUZA; SILVA; CARVALHO, 2010).

### 2.1 STEPS OF INTEGRATIVE REVIEW

The review was conducted in six methodological stages, according to the model proposed by Mendes, Silveira and Galvão (2008):

1. **Elaboration of the guiding question;**
2. **Definition of inclusion and exclusion criteria;**
3. **Search and selection of studies in databases;**
4. **Data extraction and organization;**

5. **Analysis and critical interpretation of the results;**
6. **Synthesis and presentation of findings.**

The guiding question was defined as:

*What is the scientific evidence published in the last ten years that addresses the efficacy and safety of empagliflozin associated with metformin in the treatment of type 2 diabetes mellitus?*

## 2.2 SEARCH STRATEGY

The search for studies was carried out between **October and December 2025**, using the following **electronic scientific databases**: **PubMed**, **SciELO, ScienceDirect**, **Scopus,** and **Google Scholar**.

The **controlled and uncontrolled descriptors** (in Portuguese and English) were used, combined by the Boolean operators *AND* and *OR*:

- ("Empagliflozin" OR "Empagliflozin") AND
- ("Metformin" OR "Metformin") AND
- ("Type 2 Diabetes Mellitus") AND
- ("Efficacy" OR "Efficacy") AND
- ("Safety").

The DeCS/MeSH descriptors **were also used**: *Empagliflozin*, *Metformin*, *Type 2 Diabetes Mellitus*, *Drug Therapy Combination*, *Treatment Outcome*, *Safety*.

## 2.3 INCLUSION AND EXCLUSION CRITERIA

**Inclusion Criteria:**

- Articles published between **2015 and 2025**;
- Studies available in **Portuguese, English or Spanish**;
- Studies that evaluated **the efficacy and/or safety of the empagliflozin/metformin combination**;
- Clinical trials, systematic reviews, meta-analyses and comparative studies;
- Studies conducted with **adult humans** diagnosed with T2DM.

**Exclusion Criteria:**

- Duplicate jobs in more than one database;
- Studies carried out with animals or in *vitro models*;
- Theses, dissertations, editorials, letters to the editor and congress abstracts;

- Articles that addressed only empagliflozin or metformin alone, without association.

## 2.4 STUDY SELECTION PROCESS

The screening of the articles was carried out in three phases:

1. **Reading of titles and abstracts**, to exclude studies unrelated to the theme;
2. **Complete reading of the eligible texts**, with application of the inclusion and exclusion criteria;
3. **Extraction of relevant data** and recording of information in a summary table, containing: author, year, country, objective, methodology, main results and conclusions.

Of the studies initially identified, **11 articles** met all the criteria and were included in the final review.

## 2.5 DATA ANALYSIS AND SYNTHESIS

The data were analyzed in a descriptive and interpretative manner, with a focus on identifying convergences and divergences between the reviewed studies. The information was organized into comparative tables and summary tables, grouping results according to efficacy (glycemic control, reduction of HbA1c, body weight, blood pressure) and safety (adverse events, hypoglycemia, tolerability, and renal and cardiovascular safety).

The results were discussed in light of current evidence and the recommendations of the Guidelines of the Brazilian Diabetes Society (SBD, 2023) and the International Diabetes Federation (IDF, 2023), with an emphasis on the clinical applicability of the therapeutic combination studied.

## 2.6 ETHICAL ASPECTS

As this is a bibliographic research based on secondary sources, without direct involvement of human beings, there was no need to submit it to the Research Ethics Committee, according to Resolution No. 510/2016 of the National Health Council (BRASIL, 2016).

## 3 RESULTS

### 3.1 SUMMARY OF THE INCLUDED STUDIES

After applying the inclusion and exclusion criteria, 11 scientific studies published between 2015 and 2025 were selected. Among these, six randomized clinical trials, three systematic reviews, one comparative study, and one cost-effectiveness study comprised the final sample analyzed.

The studies together included approximately 6,000 adult patients diagnosed with type 2 diabetes mellitus treated with different regimens involving the empagliflozin/metformin combination, alone or in combination with other oral antidiabetic drugs.

The publications were obtained from the PubMed, SciELO, ScienceDirect and Scopus databases, including research conducted in Germany, China, South Korea, the United Kingdom, India and Brazil. This geographic diversity increases the representativeness of the results and confers external robustness to the evidence analyzed.

The studies mainly addressed the clinical efficacy and safety profile of the combination, considering variables such as reduced glycated hemoglobin (HbA1c), body weight, blood pressure, adverse events, as well as cardiovascular and renal effects. This methodological plurality supports a comprehensive and representative integrative analysis of the contemporary literature on the subject.

### 3.2 CLINICAL EFFICACY OF THE EMPAGLIFLOZIN/METFORMIN COMBINATION

The reviewed studies consistently demonstrate that the empagliflozin/metformin combination promotes superior glycaemic control than metformin monotherapy, with significant reductions in HbA1c and improvements in multiple metabolic parameters.

Hadjadj et al. (2016) identified an average reduction of 1.85% in HbA1c after 24 weeks of combined treatment, while Zhong et al. (2016) reported a significant improvement in fasting and postprandial blood glucose, associated with a reduction in body weight and systolic blood pressure. Goldman et al. (2018) and Park et al. (2024) corroborated these findings, demonstrating maintenance of glycemic control for up to two years, in addition to preserving the function of pancreatic β cells and reducing insulin resistance.

Although convergent, the studies show variations in the doses of empagliflozin (10 mg and 25 mg daily) and in the duration of treatments (from 12 to 104 weeks), which may influence the magnitude of the effects observed. Still, the results support that the combination exerts synergistic and complementary effects, metformin reduces hepatic glucose

production, while empagliflozin promotes renal glucose excretion, resulting in broader and more sustainable glycemic control.

### 3.3 SAFETY AND TOLERABILITY PROFILE

The empagliflozin/metformin combination showed a high safety profile and good clinical tolerability, corroborated by all included studies.

Kedia et al. (2016) and Goldman et al. (2018) reported a low incidence of serious adverse events, highlighting as more common mild genital infections and polyuria, predictable and self-limiting effects related to the glycosuretic action of SGLT2 inhibitors.

Wazir and Rehman (2022) observed that the introduction of empagliflozin in patients with suboptimal control on metformin and sitagliptin did not increase the occurrence of hypoglycemia, lactic acidosis, or renal dysfunction. Ji et al. (2023) reported similar results in Chinese patients, including those who used insulin concomitantly, demonstrating the safety of the association in different therapeutic regimens.

Some studies, however, have identified a slight increase in the incidence of urinary tract infections, especially in women, although without the need for treatment discontinuation (ZHONG et al., 2016). These findings reinforce that the combined use has a superior safety profile to other antidiabetic therapies, especially because it does not induce hypoglycemia or weight gain, which are common undesirable effects on sulfonylureas and insulin.

### 3.4 ADDITIONAL METABOLIC AND SYSTEMIC EFFECTS

In addition to glycemic control, empagliflozin/metformin has demonstrated additional metabolic and systemic benefits.

Park et al. (2024) reported a significant reduction in body fat and albuminuria, suggesting a potential early renoprotective effect. The study published by MDPI (2025) expanded on these findings, observing an improvement in liver and lipid markers, with a reduction in triglycerides and an increase in HDL-cholesterol, which suggests a possible protective role against metabolism-associated fatty liver disease (MASLD).

These effects seem to be related to improved insulin sensitivity and hepatic modulation of glucose and lipid metabolism, mechanisms that go beyond glycemic control alone. However, the literature is still limited regarding the duration and consistency of these effects in different populations, pointing to the need for longitudinal studies that evaluate the long-term metabolic and hepatorenal impact.

Results from large multicenter trials, such as the Jardiance Study Group (2020), complement this evidence by demonstrating significant reduction in major cardiovascular events (MACE) and improvement of renal function in patients treated with empagliflozin. These findings reinforce the pleiotropic effect of the association, which acts positively on multiple organ systems.

### 3.5 COMPARISON WITH OTHER THERAPIES AND CLINICAL IMPLICATIONS

Comparative studies have shown that empagliflozin/metformin has equal or superior efficacy to other therapeutic combinations, with a more favourable safety profile.

Khan et al. (2022) observed similar glycemic efficacy between empagliflozin/metformin and vildagliptin/metformin, but with better tolerability and lower weight gain in the empagliflozin group. Ramos et al. (2020) demonstrated that the association offers a better cost-effectiveness ratio than oral semaglutide and canagliflozin, especially in patients with moderate to high cardiovascular risk.

This evidence supports the recommendations of the Brazilian Diabetes Society Guidelines (SBD, 2023) and the International Diabetes Federation (IDF, 2023), which position empagliflozin, alone or in combination with metformin, as a preferred second-line option after initial treatment failure.

In the Brazilian context, however, the incorporation of this therapy into the Unified Health System (SUS) still faces economic and logistical challenges. However, the data analyzed indicate that the rational use of this combination can reduce complications and hospitalizations, positively impacting the sustainability of the system and the quality of life of patients.

### 3.6 LIMITATIONS OF THE LITERATURE AND RESEARCH GAPS

Despite the consistency of the evidence, this review identified some relevant limitations. Most studies have a short follow-up duration (less than two years) and a moderate sample size, which restricts the generalizability of the results. In addition, there is a paucity of Latin American studies and a lack of long-term comparative analyses involving different age groups and levels of glycemic control.

Future research should include longer-term multicenter trials, incorporating regional cost-effectiveness analyses and robust clinical outcomes (such as cardiovascular mortality

and progression of diabetic nephropathy), in order to consolidate the evidence on the applicability of empagliflozin/metformin in different socioeconomic realities.

### 3.7 INTEGRATIVE CONCLUSION OF THE RESULTS AND DISCUSSION

The findings of this integrative review answer the guiding question, demonstrating that the empagliflozin/metformin association is effective, safe, and metabolically beneficial in glycemic control in patients with type 2 diabetes mellitus.

Combined therapy provides a significant reduction in HbA1c, improvement of cardiovascular and renal parameters, and has a favorable safety profile, with a low incidence of serious adverse events.

In the clinical and public health scenario, the use of this combination represents a rational, cost-effective therapeutic strategy in line with international guidelines, with the potential to reduce morbidity and mortality associated with DMT2.

Still, the literature reinforces the need for new long-term studies, especially in Latin American populations, to strengthen the scientific evidence and expand the applicability of this association in the global management of type 2 diabetes.

## 4 CONCLUSION

The objective of this integrative review was to analyze the scientific evidence published in the last ten years on the efficacy and safety of the empagliflozin/metformin (Jardiance Duo) combination in glycemic control in patients with type 2 diabetes mellitus (T2DM).

The analysis of the 11 included studies showed that the combination therapy promotes significant reductions in glycated hemoglobin (HbA1c), better control of fasting and postprandial blood glucose, as well as additional benefits on body weight, blood pressure, and renal and lipid parameters. These findings confirm the synergistic and complementary effect between the mechanisms of action of the two drugs, favoring a more comprehensive and sustainable glycemic control compared to metformin monotherapy.

Regarding safety and tolerability, the association presented a favorable profile, with a low incidence of serious adverse events and no increase in hypoglycemia. The most recurrent effects were mild genital infections and polyuria, which are usually self-limiting, which reinforces the safety of therapy for long-term use, including in patients using other oral antidiabetic drugs or insulin.

In addition to the glycemic impact, additional metabolic and systemic effects were observed, such as improvement in liver, lipid, and renal markers, suggesting potential cardiovascular and renoprotective benefits, in line with the evidence from large international multicenter trials.

In the clinical and public health context, the results support that the combined therapy empagliflozin/metformin is an effective, safe, and cost-effective strategy, capable of reducing chronic complications and hospitalizations related to T2DM, in addition to optimizing therapeutic approaches and improving the quality of life of patients. However, long-term studies are still needed, especially in Latin American populations, that evaluate broader clinical outcomes, such as cardiovascular mortality, progression of diabetic nephropathy, and economic impact on public health systems.

Therefore, it is concluded that the empagliflozin/metformin association represents a relevant and promising therapeutic option in the management of type 2 diabetes mellitus, integrating efficacy, safety, and economic viability. Its adoption, when aligned with national and international guidelines, can strengthen evidence-based clinical practices and contribute significantly to the advancement of comprehensive care for people with diabetes.

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