Hrvat. čas. zdr. znan. 2025; 5: 24-31
https://doi.org/10.48188/hczz.5.1.4

Izvorni rad
Original articles

ANALYSIS OF SIDE EFFECTS OF METFORMIN IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

BOJANA JOVOVIĆ[1], MARIETA BUJAK[1], MLADEN KRNIĆ[2]

Objective: To determine the frequency of side effects among various metformin formulations and to examine their association with the method of drug administration, the type of therapy prescriber, and patient education level.

Participants and Methods: The study included 126 patients with type 2 diabetes mellitus, who were assessed using a specifically structured questionnaire. The survey was conducted at the outpatient clinic of the Regional Center for Endocrinology, Diabetology and Metabolic Disorders, University Hospital Centre Split.

Results: Adverse effects caused a change in therapy in 15.4% of patients. A statistically significant decrease in adverse effects was observed when comparing the initial and current treatment (p = 0.004). Monotherapy with metformin preparations, whether Immediate Release (IR) or Extended Release (ER), significantly more frequently caused adverse effects compared to comb preparations of metformin and other drugs (SGLT2 inhibitors, DPP-4 inhibitors) (p = 0.007). Depending on meal timing, 63.2% of patients took the medication correctly, while 27.2% took it incorrectly. Adverse effects occurred in 10.13% of patients who took the medication correctly, and in 15.22% of those who took it incorrectly. Specialists prescribed therapy for 89.6% of patients, while family medicine physicians prescribed therapy for 10.4%. Regarding patient education about medication intake related to meals, adverse effects were reported in 25% of poorly informed patients, while the adverse effects decreased from 25.4% to 11.47% in better informed patients.

Conclusion: Metformin preparations differ in the frequency of adverse effects, with monotherapy metformin preparations, whether Immediate Release (IR) or Extended Release (ER), more frequently causing adverse effects compared to comb-preparations of the same drug. No statistically significant difference was found in the occurrence of adverse effects depending on the prescribing physician. There is no statistically significant frequency of adverse effects among patients who were poorly informed about medication intake concerning meals, nor is there a statistically significant difference in adverse effects associated with inadequate therapy intake concerning meals.

Keywords: DIABETES MELLITUS TYPE 2, METFORMIN, PATIENT EDUCATION, SIDE EFFECTS

Introduction

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder characterized by persistently elevated blood glucose levels due to insulin resistance and a relative insulin deficiency (1). According to the World Health Organization, approximately 828 million adults were living with diabetes in 2022, with the vast majority having type 2 diabetes (2, 3). The global prevalence continues to rise, especially in low- and middle-income countries, where access to prevention and treatment is limited. It is projected that by 2050, the number of people with diabetes will exceed 1.3 billion, with type 2 diabetes accounting for the largest.

In Croatia, 327,785 people are officially registered with diabetes, but estimates suggest the actual number may reach up to 500,000 (5, 6).

Type 2 diabetes is more common in men aged 25 to 69 years and is driven by obesity (high Body mass index (eng. BMI)), physical inactivity, unhealthy diet, older age, and genetic predisposition (7). Insulin resistance leads to β-cell failure, resulting in poor glycemic control, inflammation, oxidative stress, endothelial dysfunction, and ultimately vascular damage and its associated complications (8).

Diagnosis of T2DM is based on standard biochemical criteria, while treatment focuses on non-pharmacological measures, including nutritional therapy and physical activity. However, when lifestyle changes are insufficient to achieve glycemic targets, pharmacological treatment is initiated (9, 10).

[1]Medicinski fakultet Sveučilišta u Splitu
[2]Medicinski fakultet Sveučilišta u Splitu, Klinički bolnički centar Split

Corresponding author:
Marieta Bujak, dr. med. dent.
Medicinski fakultet Sveučilišta u Splitu
21000 Split, Šoltanska 2A
E-mail: marietab9@gmail.com

Metformin is the primary representative of biguanides and the first-line treatment for type 2 diabetes mellitus (T2DM). It is derived from the plant Galega officinalis, which has been known since the Middle Ages (11, 12). Unlike insulin secretagogues, metformin does not directly stimulate insulin secretion from β-cells, which contributes to its low risk of hypoglycemia. Its primary mechanism involves suppressing hepatic glucose production through activation of AMP-activated protein kinase, which also enhances peripheral insulin sensitivity (13-15). It partially slows intestinal glucose absorption and reduces renal gluconeogenesis (12-15). Metformin is not metabolized and is excreted unchanged by the kidneys, with a half-life of about 5 hours. Due to gluconeogenesis inhibition, it may increase the risk of lactic acidosis, especially in patients with renal insufficiency. It is used with caution and at reduced doses when creatinine clearance is below 60 mL/min, and it is contraindicated when clearance is below 30 mL/min.Additionally, metformin does not cause weight gain and may cause mild weight loss in some cases; it also has documented cardiovascular benefits (10n). Contraindications include severe liver insufficiency, pancreatitis, chronic alcoholism, malnutrition, hypoxic states, and old age (15-17). Therapy begins at 500 mg/day, gradually increasing to 2,000 mg/day based on tolerance (17). The most common side effects of metformin are gastrointestinal - diarrhea, nausea, vomiting, abdominal discomfort, and anorexia. They occur in up to 30% of patients, are dose-dependent, and usually transient. In 3-5% of patients, they persist and require therapy discontinuation. Less common side effects include chest discomfort, headache, diaphoresis, hypoglycemia, weakness, and rhinitis. Long-term use may reduce vitamin B12 levels, especially in anemia and peripheral neuropathy - monitoring and possible supplementation are recommended. The most severe complication is lactic acidosis (15, 18).

This study aims to determine the frequency of side effects of metformin preparations and relate them to the method of taking prescribed therapy, pres-

Poštovani ispitanici, ovom anketom želimo steći uvid o vašoj terapiji na metforminu kako bi pronašli koincidenciju s nuspojavama na isti lijek. Anketa je u svrhu izrade diplomskog rada. Svi odgovori i podaci su isključivo anonimni. Hvala.

ANKETA

Ime i prezime:

Dob:

Spol:

Težina:

BMI:

Obiteljska anamneza za šećernu bolest(Je li netko u obitelji imao šećernu bolest?): DA ili NE

Trajanje šećerne bolesti(Kada je dijagnosticirana?):

Zadnja izmjerena vrijednost HbA1c:

Zadnja izmjerena vrijednost šećera na tašte:

Zadnja izmjerena vrijednost postprandijalno (nakon jela):

Prosječna izmjerena vrijednost postprandijalno (nakon jela):

Zadnje izmjereni kreatinin:

Terapija i doza šećerne bolesti:

Otkada je uzimate:

- **Što ste uzimali prije ove terapije?**
- **Koliko dugo ste je uzimali?**
- **Zašto ste promijenili terapiju?**

Koja vam je bila prva terapija za liječenje šećerne bolesti:

- **Koliko dugo ste je uzimali?**
- **Zašto ste promijenili terapiju?**
- **Je li bilo kakvih nuspojava?**

Način uzimanja terapije(Kad ste jučer uzeli pripravak metformina?):

1. Prije jela 2. Poslije jela 3. Za vrijeme jela 4. Nešto drugo

Jeste li u posljednjih tjedan dana preskočili terapiju?

Preskačete li inače terapiju?

Ako DA, kada ste je zadnji put preskočili?

Koliko puta ste je preskočili?

Ima li neka vrsta jela utjecaja na to kako i kada popijete lijek?

Jeste li u zadnjih 7 dana imali mučninu, povraćanje, proljev, okus metala u ustima?

Ako DA; Kad se javi?

Koliko traje?

Jeste li smanjivali terapiju?

Tko vam je propisao ovaj lijek? Liječnik obiteljske medicine, specijalist endokrinolog/dijabetolog, drugi specijalist?

Ostale bolesti:

Ostale terapije:

Kako biste ocijenili svoju informiranost o:

Šećernoj bolesti	**loše**	**1**	**2**	**3**	**4**	**5**	**dobro**
Svrsi liječenja ovim lijekom	**loše**	**1**	**2**	**3**	**4**	**5**	**dobro**
Potencijalnim nuspojavama	**loše**	**1**	**2**	**3**	**4**	**5**	**dobro**
Načinu uzimanja	**loše**	**1**	**2**	**3**	**4**	**5**	**dobro**

Jeste li obavješteni o načinu uzimanja lijeka? DA NE

Tko vam je dao upute?

a) Medicinska sestra u ambulanti LOM-a

b) Medicinska sestra u centru za dijabetes

c) Liječnik obiteljske medicine

d) Liječnik specijalist

e) Liječnik - drugi

f) Netko drugi

Ako je uzimano više pripravaka metformina koji oblik preferira. Zašto?

Zašto je dobro/loše informiran?

criber specialty, and patient education using a specially designed questionnaire.

Materials and Methods

Participants

The participants in this cross-sectional study were individuals diagnosed with type 2 diabetes mellitus who are currently or have been treated with some form of metformin preparation. A total of 126 participants were enrolled, including 56 females and 70 males. All included participants are being treated for type 2 diabetes mellitus at the Regional Center for Diabetes, Endocrinology, and Metabolic Disorders of the Clinical Hospital Center Split and met the inclusion and exclusion criteria. Before the survey, participants were informed about the purpose of the study, and subsequently provided informed consent. During and after the study, the rights and personal data of participants were protected under patient protection laws, the Code of Medical Ethics, and the Declaration of Helsinki. The study was approved by the Ethics Committee of the Clinical Hospital Center Split (Class: 500-03/22-01/59, Reg. No.: 2181-147/01/06/M.S.-22-03, 23 May2022). Inclusion criteria were age between 18 and 99 years, diagnosis of type 2 diabetes mellitus, and prescribed therapy containing metformin. Exclusion criteria included refusal to provide informed consent and patients diagnosed with gestational diabetes mellitus.

Organization and Description of the Study

For the study, a specially designed questionnaire (Attachment 1) was created, consisting of four main groups of questions. The first group concerned general data including name and surname, sex, age, weight, and body mass index (BMI). The second group gathered data related to diabetes, including questions about family history of diabetes, duration of diabetes, latest measured HbA1c and creatinine values, latest fasting and postprandial glucose levels, and average postprandial glucose value. The third group focused on treatment of diabetes with metformin preparations and other medications, including: current diabetes therapy, drug doses and duration of treatment, previous therapy including duration and reasons for changes, initial diabetes therapy, duration, reasons for changes, presence of adverse effects, type, duration, and timing of adverse effects in the past 7 days if present, method of drug administration, omission of therapy within the last 7 days before completing the questionnaire and general therapy omissions, impact of meals on drug intake, prescriber of therapy, as well as other chronic diseases and concomitant chronic treatment. The fourth and final group of questions focused on patient education, specifically their awareness of diabetes mellitus, the purpose of treatment, potential adverse effects, and the timing and consistency of therapy in relation to meals. His category also included questions about the source of patient information regarding treatment, their self-assessment of the adequacy of information, and reasons for such assessment.

Statistical Analysis

The collected data were processed using Microsoft Office software, Microsoft Word for text processing, and Microsoft Excel for tabular presentation. Statistical analysis was conducted using SPSS software version 28.0 (IBM Corp., Armonk, NY). Absolute numbers and percentages were used to describe categorical data. Median and interquartile range were used to describe numerical data, while standard deviation was applied only to assess informativeness. Chi-square test and Fisher's exact test were used for comparison of categorical variables. Results were interpreted at a significance level of $P < 0.05$.

Results

The study included 126 patients who are currently or have previously been treated with metformin. Their basic characteristics are presented in Table 1.

One female patient no longer uses therapy, while the number of participants currently on therapy with the mentioned medications is 125. The most commonly used formulation of the drug was metformin monotherapy with immediate-release (35 patients or 28%), followed by IR combination of metformin and SGLT2 inhibitor (30 patients or 24%). The third most common formulation was also IR combination of metformin and DPP-4 inhibitor with 24 users (19.2%).

The median duration of current therapy was 2 years, with an interquartile range of 0.5 to 5 years. Regarding the timing of therapy intake, 79 (63.2%) of patients take metformin after meals as recommended,26 (20.8%) take it before meals, 12 (9.6%) during meals, and the remaining 8 (6.4%) regardless of meals or at other times of the day.

Table 1.
Basic characteristics of the participants

Parameter	Value (Median, IQR)
Sex, n (%)	
Men	70 (55.60)
Women	56 (44.40)
Age (years)	66 (60-71)
Body weight (kg)	88 (75.75-95)
Body mass index (BMI) (kg/m²)	28 (25.33-31.53)
Duration of diabetes (years)	10 (5-15)
HbA1c (%)	7.1 (6.40-7.70)
Last fasting plasma glucose (mmol/L)	6.85 (6.00-7.83)
Last postprandial plasma glucose (mmol/L)	8.1 (6.63-9.95)
Average postprandial plasma glucose (mmol/L)	8 (7-9)
Creatinine (µmol/L)	71.5 (61.75-88)

Abbreviations: IQR = interquartile range; HbA1c = glycated hemoglobin; BMI = body mass index.

Table 2.
Presence of adverse effects depending on the mode of administration

Variables (N=125)	Presence of Adverse Effects	P*
Correct administration	8/79 (10.13%)	0.407
Incorrect administration	7/46 (15.22%)	

*Fisher's exact test

Table 3.
Presence and absence of adverse effects during the first and current therapy

Presence of adverse effects	First therapy (N=126)	Current therapy (N=125)	P†
Yes	32	15	0.004

†Chi-square test

Table 4.
Analysis of adverse effects during current therapy according to prescriber

Prescriber	Current Therapy (N=125) Adverse Effects Presence, n/N (%)	P*
Diabetologist	14/112 (12.5%)	0.518
Family Medicine Physician	1/13 (7.7%)	
Prescriber	First Therapy (N=119) Adverse Effects Presence, n/N (%)	P*
Diabetologist	29/112 (25.9%)	0.518
Family Medicine Physician	3/13 (13%)	

*P-value calculated using Fisher's exact test

The occurrence of adverse effects depending on correct and incorrect medication administration in relation to meals are presented in Table 2. However, the difference between the group who took the medication correctly, after meal (79), and incorrectly, before, during the meal or remaining (46) was not statistically significant ($P = 0.407$).

Out of 126 participants who use or have used metformin preparations, 91 (72.22%) had previously used another form of metformin before the current therapy. Metformin monotherapy IR preparation was most commonly used as the initial therapy, taken by 52 patients (41.27%), while only 8 (6.35%) currently use it. The number of patients on other type of metformin monotherapy with extended release also decreased from 11 (8.73%) to 3 (2.38%), while the use of metformin combination with DPP-4 inhibitor significantly increased, from 1 patient (0.79%) as initial therapy to 30 patients (23.80%) currently. The median duration of the first therapy was 2 years (IQR 1-2 years), and of previous therapy 3 years (IQR 1-8 years). A statistically significant difference ($P = 0.004$) in adverse effect frequency between the first and current therapy was demonstrated in Table 3.

Reasons for discontinuation of previous therapies were investigated. Fourteen patients (15.4%) stopped therapy due to adverse effects, 73 (80.2%) due to improved glycemic control with the new preparation, and 4 (4.4%) changed therapy for other reasons, such as drug interactions or financial reasons.

Current metformin therapy was prescribed by an endocrinology and diabetology specialist for 112 patients (89.6%), and by a general practitioner for 13 patients (10.4%). There was no statistically significant difference in the frequency of adverse effects between patients prescribed therapy by a specialist and those prescribed by a general practitioner (Table 4).

Diarrhea was the most common adverse effect in all three observed categories, occurring in all patients who reported adverse effects on previous therapy and in 46.6% of those with adverse effects on current therapy. Nausea was the second most common adverse effect, recorded in 57.14% of patients with adverse effects on previous therapy and 53.3% of those on current therapy. Metallic taste was reported by one patient with adverse effects on current therapy, one on previous therapy, and four patients with adverse effects on the first therapy.

Table 5. presents the adverse effects of current metformin therapy depending on the preparation used In general, the use of metformin monotherapy-whether immediate-release or extended-release was associated with a significantly higher frequency of adverse effects compared to combination preparations of metformin with SGLT2 or DPP-4 inhibitors ($P = 0.007$).

Regarding patients' self-assessed knowledge about awareness of diabetes mellitus, treatment purpose, adverse effects, and therapy intake, participants rated their knowledge on a scale from 1 (insufficient) to 5 (excellent). The results are shown in Table 6.

Additionally, participants were divided into two groups based on their ratings of knowledge about therapy intake: those scoring 1 to 3 were classified as less informed, while those scoring 4 or 5 were classified as better informed. The occurrence of adverse effects during the first therapy was approximately equal in both groups (around 25%), whereas during the current therapy adverse effects were less frequent in the better-informed group (11.47%) compared to the less informed group (25%).

Table 5.
Analysis of adverse effects during current metformin therapy according to preparation

Therapy Type	Adverse Effects Presence, n/N (%)	P†
Siofor®	6/35 (17.14%)	0.270
Metformin+ SGLT2 /DPP-4 inhibitors	9/90 (10.0%)	
Glucophage®	6/21 (28.57%)	0.010
Metformin+ SGLT2 /DPP-4 inhibitors	9/104 (8.65%)	
Glucophage®, Siofor®, Gluformin ®	12/59 (20.34%)	0.007
Metformin+ SGLT2 /DPP-4 inhibitors	3/66 (4.55%)	

†P-value calculated using χ^2 test

Table 6.
Self-assessment of awareness

Parameter	Median ± SD
Awareness of diabetes mellitus	3.78 ± 0.97
Awareness of treatment purpose	3.42 ± 1.01
Awareness of adverse effects	3.48 ± 1.09
Awareness of the administration method	4.79 ± 0.48

Scale: 1-insufficient, 2-sufficient, 3-good, 4-very good, 5-excellent.

Discussion

The results of this study showed that as many as 15.4% of patients discontinued therapy due to side effects, placing our findings within the range reported in other relevant studies, although discontinuation rates vary (19, 20). According to the study conducted in the United Kingdom, 35.9% of new metformin users and 23.1% of continuous users discontinued therapy within 12 months, while the global DISCOVER study found that 15.1% of patients who started metformin therapy discontinued treatment when initiating second-line therapy (21, 22). A study conducted in Hong Kong reported that 22.3% of patients with severe renal insufficiency (eGFR <30) discontinued therapy within the first 6 months, highlighting the need for an individualized approach (23).

The most common side effects in this study were diarrhea, nausea, vomiting, and metallic taste, consistent with results from a systematic review and meta-analysis encompassing 71 randomized controlled trials (24). A decrease in the frequency of side effects was observed following therapy modification-side effects occurred in 25.6% of patients upon initial prescription of metformin, compared to 12% during the current therapy. Saluja M. et al. also demonstrated that most of the mentioned side effects appear in the initial phase of treatment. This is likely due to temporal adaptation to the active substance, dose adjustment, and the "finding" of the formulation best suited to the individual patient. This aligns with diabetologists' observations and recommendations that metformin should not be dismissed as an option upon the occurrence of side effects, but that gradual patient acclimatization or changing the preparation may achieve the desired outcome (25).

While Glucophage® was identified in our study as the preparation with the highest incidence of side effects with statistical significance (p=0.010), the previously mentioned research showed the highest side effect occurrence with Siofor® therapy (19). Such results indicate the need for study expansion. A systematic review and meta-analysis investigating the side effect profiles of various metformin formulations demonstrated that side effects are significantly less frequent with extended-release (ER) preparations compared to immediate-release (IR) formulations (26). Similar findings were recorded in a large prospective study conducted in six Asian countries involving 3556 patients. This study showed that metformin XR was well tolerated, with gastrointestinal side effects occurring in only 3.3% of patients, and 97.4% of patients completed 12 weeks of treatment without interruption due to side effects (27). Comparing this with data from our study, which also included subjects on extended-release metformin therapy (Glucophage® XR), the results appear consistent, as only the immediate-release formulation (Glucophage® IR) demonstrated a significant side effect prevalence, while the XR form did not show such a trend. However, the sample size does not allow for definitive, statistically significant conclusions regarding these differences. All these results confirm the initial hypothesis about differences in side effect incidence between formulations regardless of dose.

We also observed a group of the most commonly used monotherapy metformin preparations and found a statistically significant difference in side effect incidence among these (p=0.007) compared to other comb-preparations including SGLT2 / DPP-4 inhibitors. On the other hand, some studies argue that these combinations often allow for lower metformin doses, reducing its gastrointestinal side effects, but warn of additional side effects arising from the other component drug (28, 29). This phenomenon of higher side effect frequency with metformin monotherapy preparations compared to comb-preparations could be explained by the fact that treatment typically begins with monotherapy, when side effects are more common. In contrast, comb-preparations are usually introduced after patients have already adapted to metformin and potentially found the formulation that suits them best.

Analysis of data obtained from patient self-assessment regarding their education on certain questions (awareness of diabetes mellitus, treatment purpose, adverse effects and therapy intake regarding meals) did not yield statistically

significant correlations with side effect occurrence. It should be noted that the question regarding informing about the drug administration regarding mealsitself is not amenable to adequate statistical analysis due to a pronounced imbalance between poorly and well-informed patients. There is a signal that side effect incidence in initial therapy remained unchanged, as well as during current therapy, in the poorly informed group (25%), while in the better-informed group it decreased from 25% to 11.47% during current therapy. Such a result suggests that better education enables a reduction in side effect frequency, consistent with other studies on the topic (19, 30-32).

Bakovic J., in his study, found a statistically significant association between improper metformin intake timing relative to meals (recommended after meals) and side effect occurrence, whereas our study did not confirm these results despite some indications (10% vs. 15%) (19). This may be due to a substantially higher proportion of respondents adhering to proper drug use instructions (63.2% after meals), including those who took the drug in a slightly less correct manner (9.6% during meals). Such distribution could be attributed to the fact that all respondents were surveyed at the Diabetes Center of KBC Split, where they are directly informed by endocrinologists, diabetologists, and nurse educators during regular check-ups.

Badi S. et al. also emphasize the importance of adherence to instructions on taking metformin with food, especially when supported by education provided by clinical pharmacists (33). Unlike our findings, other studies with much larger samples found that only 34% of metformin users adhere to proper therapy administration rules, which is suboptimal. This can be explained by a range of barriers to achieving optimal treatment related to patients, physicians, and the treatment itself (including psychological and physical difficulties such as swallowing large tablets, gastrointestinal disturbances, polypharmacy due to multiple comorbidities common in diabetes) (34, 35).

For the above reasons, since nearly all participants were patients of the Diabetes Center, the hypothesis regarding side effect incidence depending on the prescribing physician could not be confirmed or statistically analyzed (due to an inadequate ratio). Current metformin therapy was prescribed by an endocrinology and diabetology specialist for 112 patients (89.6%), and for 13 patients (10.4%) it was prescribed by a family medicine specialist. This hypothesis should be tested on a larger sample, including more patients regularly monitored by family medicine specialists. Regarding other studies on this topic, although specific differences in metformin side effects prescribed by specialists versus general practitioners are not clearly defined, there are significant differences in prescribing patterns between them. Specialists more frequently prescribe metformin and advanced therapies, while general practitioners more commonly prescribe monotherapy and do so less frequently in patients with complex disease profiles (36-38).

Although this study confirmed two out of five hypotheses, the obtained results can serve as a foundation for further research aimed at reducing complications and improving individualized treatment approaches. Discontinuation of prescribed therapy due to side effects represents a serious challenge in achieving optimal disease control and preventing long-term complications. Although this challenge is a global issue, this study contextualizes it within the Croatian regional setting. Data on side effect frequency can help improve therapeutic guidelines and educational programs for patients and reduce therapy discontinuation.

The strength of the study lies in the representativeness of the sample, clearly defined patient population, use of a detailed and structured questionnaire, adequate statistical analysis, and ultimately, the clinical relevance and direct applicability of the study in general practice.

Limitations of this study, in addition to the previously mentioned population sample from a single institution and uneven data distribution, include the inability to prove causality, risk of response bias in the questionnaire (including intentional provision of socially desirable answers), and lack of control for confounding factors potentially affecting side effect occurrence, such as metformin dose, diet type, concomitant medications, chronic disease severity, etc.

Conclusions

Different metformin formulations, regardless of dose, differ in the occurrence of side effects. Monotherapy metformin preparations, whether IR or ER, show a higher frequency of side effects compared to comb-preparations of metformin and SGLT2 or DPP-4 inhibitors. Furthermore, there is no statistically significant difference in the occurrence of side effects depending on the prescribing physician. Additionally, a statistically significantly higher frequency of side effects was not demonstrated among patients who were poorly informed about medication intake in relation to meals, nor was any statistically significant difference found in cases of improper therapy intake concerning meals.

Abbreviations:

DM - Diabetes mellitus
IDF - International Diabetes Federation
IR - Immediate Release
ER - Extended Release
T1DM - Type 1 diabetes mellitus
T2DM - Type 2 diabetes mellitus
SGLT2 - Sodium-glucose co-transporter type 2 in the proximal tubules
ADA - American Diabetes Association
OGTT - Oral glucose tolerance test
FPG - Fasting plasma glucose
WHO - World Health Organization
HHS - Hyperglycemic hyperosmolar state
DKA - Diabetic ketoacidosis
BMI - Body mass index

NOVČANA POTPORA/*FUNDING*
Nema/*None*

ETIČKO ODOBRENJE/*ETHICAL APPROVAL*
Nije potrebno/*None*

SUKOB INTERESA/*CONFLICT OF INTEREST*
Autori su popunili *the Unified Competing Interest form na www.icmje.org/coi_disclosure.pdf (dostupno na zahtjev)* obrazac i izjavljuju: nemaju potporu niti jedne organizacije za objavljeni rad; nemaju financijsku potporu niti jedne organizacije koja bi mogla imati interes za objavu ovog rada u posljednje 3 godine; nemaju drugih veza ili aktivnosti koje bi mogle utjecati na objavljeni rad./

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

Literature

1. World Health Organization. Urgent action needed as global diabetes cases increase fourfold over past decades (Internet). Geneva: WHO; 2024 (cited 2025 Jun 7). Available from: https://www.who.int/news/item/13-11-2024-urgent-action-needed-as-global-diabetes-cases-increase-four-fold-over-past-decades.

2. GBD 2021 Diabetes Collaborators. Global, regional, and national burden of diabetes from 1990 to 2021, with projections of prevalence to 2050: a systematic analysis for the Global Burden of Disease Study 2021. Lancet. 2023 Jul 15; 402 (10397): 203-34. doi: 10.1016/S0140-6736(23)01301-6. Erratum in: Lancet. 2023 Sep 30; 402 (10408): 1132. Erratum in: Lancet. 2025 Jan 18; 405 (10474): 202. PMID: 37356446; PMCID: PMC10364581.

3. Khan MAB, Hashim MJ, King JK, Govender RD, Mustafa H, Al Kaabi J. Epidemiology of type 2 diabetes - Global burden of disease and forecasted trends. J Epidemiol Glob Health. 2023; 13 (1): 3-11. doi: 10.2991/jegh.k.230104.001.

4. NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in diabetes prevalence and treatment from 1990 to 2022: a pooled analysis of 1108 population-representative studies with 141 million participants. Lancet. 2024 Nov 23; 404 (10467): 2077-93. doi: 10.1016/S0140-6736(24)02317-1. Erratum in: Lancet. 2025 Apr 5; 405 (10485): 1146. PMID: 39549716; PMCID: PMC7616842.

5. Croatian Institute of Public Health. Diabetes (Internet). Zagreb: CIPH; (cited 2022 Apr 20). Available from: https://www.hzjz.hr/.

6. Croatian Institute of Public Health. Diabetes in Croatia and Worldwide 2021. Zagreb: HZJZ; 2021.

7. World Health Organization. Diabetes (Internet). Geneva: WHO; (cited 2022 Apr 20). Available from: https://www.who.int/health-topics/diabetes.

8. Vrhovac B, Jakšić B, Reiner Ž, Vucelić B. Internal medicine. 4th ed. Zagreb: Naklada Ljevak; 2008; p. 1244-64.

9. American Diabetes Association. Standards of medical care in diabetes-2024. Diabetes Care. 2024; 47 (Suppl 1): S10-28.

10. UK Prospective Diabetes Study Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). Lancet. 1998; 352 (9131): 854-65.

11. Bailey C, Day C. Metformin: its botanical background. Pract Diabetes Int. 2004; 21: 115-7.

12. Bailey CJ. Metformin: historical overview. Diabetologia. 2017; 60: 1566-73.

13. Foretz M, et al. Understanding the glucoregulatory mechanisms of metformin. Nat Rev Endocrinol. 2019; 15: 569-89.

14. Pernicova I, Korbonits M. Metformin-mode of action and clinical implications. Nat Rev Endocrinol. 2014; 10: 143-56.

15. Katzung BG, Masters SB, Trevor AJ. Basic and Clinical Pharmacology. 11th ed. Zagreb: Medicinska naklada; 2011; p. 271-2.

16. Gong L, et al. Metformin pathways: pharmacokinetics and pharmacodynamics. Pharmacogenet Genomics. 2012; 22: 820-7.

17. Kokić S, et al. Croatian guidelines for treatment of type 2 diabetes mellitus. Medix Suppl. 2011; 17: 8-34.

18. Corcoran C, Jacobs TF. Metformin. In: StatPearls (Internet). Treasure Island (FL): StatPearls Publishing; 2022 (cited 2024 May 22). Available from: http://www.ncbi.nlm.nih.gov/books/NBK518983/.

19. Baković J. Adherence to metformin and incidence of side effects in patients with type 2 diabetes (Internet) (master's thesis). Split: University of Split, School of Medicine; 2021 (cited 2024 Jun 9). Available from: https://urn.nsk.hr/urn:nbn:hr:171:081203.

20. Horsburgh S, Sharples K, Barson D, Zeng J, Parkin L. Patterns of metformin monotherapy discontinuation and reinitiation in people with type 2 diabetes mellitus in New Zealand. PLoS One. 2021; 16 (4): e0250289.

21. Tang Y, Weiss T, Liu J, Rajpathak S, Khunti K. Metformin adherence and discontinuation among patients with type 2 diabetes: A retrospective cohort study. J Clin Transl Endocrinol. 2020; 20: 100225.

22. Khunti K, Gomes MB, Kosiborod M, Nicolucci A, Pocock S, Rathmann W, et al. Metformin discontinuation in patients beginning second-line glucose-lowering therapy: results from the global observational DISCOVER study programme. BMJ Open. 2020; 10 (8): e034613.

23. Yang A, Shi M, Wu H, Lau ES, Cheung JT, Zhang X, et al. Clinical outcomes following discontinuation of metformin in patients with type 2 diabetes and advanced chronic kidney disease in Hong Kong: a territory-wide, retrospective cohort and target trial emulation study. EClinicalMedicine. 2024; 71: 102568.

24. Nabrdalik K, Skonieczna-Żydecka K, Irlik K, Hendel M, Kwiendacz H, Łoniewski I, et al. Gastrointestinal adverse events of metformin treatment in patients with type 2 diabetes mellitus: A systematic review, meta-analysis and meta-regression of randomized controlled trials. Front Endocrinol (Lausanne). 2022; 13: 975912.

25. Katzung BG, Masters SB, Trevor AJ. Basic and Clinical Pharmacology. 11th ed. Zagreb: Medicinska naklada; 2011; p. 271-2.

26. Tarry-Adkins JL, Grant ID, Ozanne SE, Reynolds RM, Aiken CE. Efficacy and Side Effect Profile of Different Formulations of Metformin: A Systematic Review and Meta-Analysis. Diabetes Ther. 2021; 12: 1901-14.

27. Kim CH, Han KA, Oh HJ, Kim SS, Lee SC, Park YH, et al. Effect of switching from metformin immediate release to metformin extended release on glycemic control and gastrointestinal side effects in patients with type 2 diabetes mellitus: a randomized controlled trial. Diabetes Metab J. 2017; 41: 135-42.

28. Silverii GA, Tognoni G, Mannucci E. Optimizing metformin therapy in clinical practice. Diabetes Obes Metab. 2024; 26 (Suppl 3): 42-54.

29. Rahelić D, Altabas V, Bakula M, Balić S, Balint I, Bergman Marković B, et al. Croatian guidelines for pharmacological treatment of type 2 diabetes. Liječ Vjesn. 2016; 138 (3-4): 107-13.

30. Špoljarić-Kršulović M, et al. Diabetes Mellitus: Pathophysiology and Management. Medix Suppl. 2015; 21: 9-18.

31. Josipović-Jelić S, et al. Pharmacotherapy of diabetes mellitus. Pharmaca. 2010; 20: 157-66.

32. Yki-Järvinen H. Thiazolidinediones. N Engl J Med. 2004; 351: 1106-18.

33. Kernan WN, Viscoli CM, Furie KL, et al. Pioglitazone after ischemic stroke or transient ischemic attack. N Engl J Med. 2016; 374: 1321-31.

34. Araki E, Kodama K. Novel therapeutic agents for type 2 diabetes mellitus. J Diabetes Investig. 2014; 5 (1): 4-11.

35. Drucker DJ. The biology of incretin hormones. Cell Metab. 2006; 3 (3): 153-65.

36. Nauck MA, Meier JJ. Incretin hormones: their role in health and disease. Diabetes Obes Metab. 2018; 20 Suppl 1: 5-21.

37. Buse JB, et al. Effects of glucagon-like peptide-1 receptor agonists on cardiovascular outcomes: a systematic review and meta-analysis. Lancet Diabetes Endocrinol. 2019; 7: 776-85.

38. Marso SP, Daniels GH, Brown-Frandsen K, Kristensen P, Mann JF, Nauck MA, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2016; 375: 311-22.

Sažetak

ANALIZA NUSPOJAVA METFORMINA U BOLESNIKA SA ŠEĆERNOM BOLEŠĆU TIPA 2

Bojana Jovović, Marieta Bujak, Mladen Krnić

Cilj: Utvrditi učestalost nuspojava kod različitih pripravaka metformina te ispitati njihovu povezanost s načinom uzimanja lijeka, propisivačem terapije i educiranošću bolesnika.

Ispitanici i metode: U istraživanju je sudjelovalo 126 bolesnika sa šećernom bolešću tipa 2, putem posebno strukturiranog upitnika. Anketiranje je provedeno u ambulanti Regionalnog centra za endokrinologiju, dijabetologiju i poremećaje metabolizma KBC-a Split.

Rezultati: Nuspojave su uzrok promjene terapije kod 15,4% bolesnika. Zabilježen je statistički značajan pad nuspojava u usporedbi prve i trenutne terapije (p=0,004). Monoterapija pripravcima metformina, bili IR (engl. Immediate Release) ili ER (engl. Extended Release), znajačno češće izaziva nuspojave u odnosu na kombinirane pripravke metformina i drugih ljekova (SGLT2, DPP-4 inhibitora) (p=0,007). Ovisno o obroku, lijek pravilno uzima 63,2% bolesnika, a neispravno 27,2%. Nuspojave su se pojavile u 10,13 % bolesnika koji su lijek uzimali pravilno, i u 15,22 % onih koji su ga uzimali nepravilno. Specijalisti su propisali terapiju za 89,6%, a liječnici obiteljske medicine za 10,4% bolesnika. Što se tiče informiranosti o načinu uzimanja terapije s obzirom na jelo, kod lošije informiranih, nuspojave su iznosile 25%, dok su među bolje informiranima iste pale s 25,4% na 11,47%.

Zaključak: Pripravci metformina se razlikuju u učestalosti nuspojava, gdje monoterapija metformisnkim pripravcima, bili IR ili ER, češće izaziva nuspojave od kombiniranih pripravaka istog lijeka. Nije dokazana statistička značajnost u pojavnosti nuspojava ovisno o propisivaču terapije. Ne postoji statistički značajna učestalost nuspojava kod pacijenata lošije informiranih o načinu uzimanja lijeka ovisno o jelu, kao ni statistička značajnost pojavnosti nuspojava kod neadekvatnog uzimanja terapije s obzirom na jelo.

Ključne riječi: DIJABETES MELLITUS TIP 2, EDUCIRANOST PACIJENTA, METFORMIN, NUSPOJAVE

Primljeno/Received: 25. 4. 2025.
Prihvaćeno/Accepted: 16. 5. 2025.