THE IMPACT OF COVID-19 PANDEMIC ON THE CONSUMPTION OF ANTIDIABETIC DRUGS IN SERBIA: A JOINPOINT TREND ANALYSIS

CORESPONDENT

Marija Milic,
marijamilic85@gmail.com

AUTHORS

Jelena Filimonovic[1,2], Zorica Stanojevic Ristic[3], Tatjana Gazibara[4], Jelena Dotlic[5,6], Jasmina Stevanovic[1], Bojan Joksimovic[7], Vladan Saponjic[8], Ivana Vukajlovic[9], Aleksandar Subaric[10], Stefan Mitic[11], Dragana Sokolovic[7], Dragana Drakul[7], Ljiljana Subaric[12], Milica Kostic[13], Marija Milic[1]
1 Department of Epidemiology, Faculty of Medicine, University of Pristina temporarily seated in Kosovska Mitrovica, Kosovska Mitrovica, Serbia;
2 Public Heath Institute of Kosovska Mitrovica, Kosovska Mitrovica, Serbia;
3 Department of Pharmacology, Faculty of Medicine, University of Pristina temporarily seated in Kosovska Mitrovica, Kosovska Mitrovica, Serbia;
4 Institute of Epidemiology, Faculty of Medicine, University of Belgrade, Belgrade, Serbia;
5 Faculty of Medicine, University of Belgrade, Belgrade, Serbia;
6 Clinic for Obstetrics and Gynecology, Clinical Center of Serbia, Belgrade, Serbia;
7 Faculty of Medicine Foca, University of East Sarajevo, Bosnia and Herzegovina;
8 Institute of Public Health of Serbia “Dr Milan Jovanovic Batut”, Belgrade, Serbia;
9 Medicines and Medical Devices Agency of Serbia (ALIMS), Belgrade, Serbia;
10 Department of oral medicine and periodontology, Faculty of Dentistry, University of Pristina temporarily settled in Kosovska Mitrovica, KosovskaMitrovica, Serbia;
11 Clinic for Surgery "Dr. Dragiša Mišović Dedinje", Clinical Hospital Center of Serbia, Belgrade, Serbia;
12 Department of dental diseases and endodontics, Faculty of Dentistry, University of Pristina temporarily settled in Kosovska Mitrovica, Kosovska Mitrovica, Serbia;
13 Student at Faculty of Medicine, University of Pristina temporarily seated in Kosovska Mitrovica, Kosovska Mitrovica, Serbia;

SUMMARY

Background: People with diabetes more often experienced severe clinical forms of COVID-19. However, it has been hypothesized that certain antidiabetic drugs may be associated with better outcomes in COVID-19 patients. The aim of this study was to analyze whether the COVID-19 pandemic influenced the change in consumption of antidiabetic drugs in Serbia.
Methods: This descriptive analysis was carried out using publicly accessible data obtained from the official website of the Medicines and Medical Devices Agency of Serbia during the period 2006-2022. The joinpoint regression analysis was applied to investigate the dynamics of antidiabetic drugs utilization over time.
Results: In the Republic of Serbia, this study analyzed the use of 28 antidiabetic drugs between 2006 and 2022.The results showed that at the beginning of the COVID-19 pandemic, there was an increase in consumption of dulaglutide (starting from 2020) and a decrease in consumption of insulin detemir (starting from 2019), insulin lispro (combined) and insulin lispro (fast-acting) (starting from 2020).
Conclusion: Our study revealed significant changes in the usage of certain antidiabetic drugs, such as increased consumption of dulaglutide and decreased use of various insulin types. These changes reflect the evolving strategies in diabetes treatment to better support patients during this global health crisis.

Key words: antidiabetic drugs, impact of Covid-19, consumption, Serbia

SRPSKI

SAŽETAK

Uvod: Osobe sa dijabetesom češće su imale teže kliničke oblike COVID-19. Međutim, postoji hipoteza da određeni antidijabetički lekovi mogu biti povezani sa boljim ishodima kod pacijenata sa COVID-19. Cilj ove studije bio je da se analizira da li je pandemija COVID-19 uticala na promenu potrošnje antidijabetika u Srbiji.
Metode: Ova deskriptivna analiza je sprovedena korišćenjem javno dostupnih podataka dobijenih sa zvaničnog sajta Agencije za lekove i medicinska sredstva Srbije u periodu 2006-2022. Regresiona analiza jointpoint je primenjena za ispitivanje dinamike korišćenja antidijabetičkih lekova tokom ispitivanog perioda.
Rezultati: U Republici Srbiji je ova studija analizirala upotrebu 28 antidijabetičkih lekova u periodu od 2006. do 2022. godine. Rezultati su pokazali da je na početku pandemije COVID-19 došlo do povećanja potrošnje dulaglutida (počev od 2020. godine) i smanjenje potrošnje insulina detemir (počev od 2019), insulina lispro (kombinovanog) i insulina lispro (brzodelujućeg) (počev od 2020.).
Zaključak: Naša studija je otkrila značajne promene u upotrebi određenih antidijabetičkih lekova, kao što su povećana potrošnja dulaglutida i smanjena upotreba različitih tipova insulina. Ove promene odražavaju strategije koje se razvijaju u lečenju dijabetesa za bolju podršku pacijentima tokom ove globalne zdravstvene krize.

Ključne reči: antidijabetički lekovi, uticaj Covid-19, potrošnja, Srbija

INTRODUCTION

The International Diabetes Federation (IDF) estimates that 537 million adults worldwide curentylive with diabetes, and that this number will rise to 643 million and 783 million by 2030 and 2045, respectively (IDF 2024). As a result,diabetes is regarded as one of the most burdensome non-communicable diseases of the 21st century.In 2021, 1.6 million deaths due to diabetes were reported, while indirectly it has been associated with 530,000 deaths from kidney disease, and contributed to 11% of deaths from cardiovascular diseases (GBD Collaborative Network 2024, WHO 2024). Based on the projections, it is expected that middle-income countries received the largest increase in dibetes prevalence of 21.1% between 2021 and 2045, followed by high-income countries (12.2%) and low-income countries (11.9%) (Sun et al.2023).

Diabetes, along with several other diseases, is considered one of the major risk factors for severe COVID-19 infection (Kabootari et al. 2022). However, because diabetes is more common in COVID-19 patients and a correlation between the two conditions has been demonstrated, researchers was invastigated the relationship between the usage of antidiabetic drugs and the severity of COVID-19 (Jang et al. 2024). Antidiabetic drugs capacity to lower cytokine production lowers cytokine levels in vascular cells, limiting endothelial damage and lowering the risk of thromboembolism and microvascular damage (Lim et al. 2021, Wiemsperger et al. 2022). Additionally, this ability inhibits the cytokine storm, which in turn reduces lung damage, a sign of severe COVID-19 infection (Wiemsperger et al. 2022). Antidiabetic drugs also enhance glucose metabolism by reducing intestinal inflammation (Bica et al. 2023). Metformin, an antidiabetic drug, has anti-inflammatory properties and may help treat COVID-19 by reducing insulin resistance, improving glucose regulation, or inhibiting reactive oxygen species in mitochondria (Gonikman and Kustovs 2023, Ouchi et al. 2022). Accordingly, it is hypothesized that some antidiabetic drugs may be associated with favorable outcomes in COVID-19. On the other hand, drugs commonly used to treat COVID-19, such as antiviral drugs and systemic corticosteroids, may worsen hyperglycemia (Lim et al. 2021).

Some newer, effective drugs for type 2 diabetes mellitus (T2D), such as sodium-glucose cotransporter 2 (SGLT2) inhibitors and glucagon-like peptide-1 (GLP-1) analogues, may exacerbate certain complications in patients with COVID-19, particularly those with underlying comorbidities. However, even if current management practices for patients with diabetes infected with SARS-CoV-2 do not differ from those in the general population, patients with diabetes require special attention due to their increased risk of complications and in-hospital death (Mirabelli et al. 2020). Given that people with diabetes are classified as at increased risk of severe COVID-19 without any distinction between types of diabetes (Smati et al. 2022), further improvements in treatment and care are needed to reduce the risk of complications.

The aim of this study was to investigate whether the COVID-19 pandemic had an impact on the consumption of antidiabetic drugs in Serbia. Given the global health crisis, it was important to assess how the pandemic might have affected healthcare practices, specifically in relation to diabetes management. This analysis would help understand shifts in treatment patterns, including any increase or decrease in drug consumption, which could be linked to factors such as increased awareness of diabetes risks during COVID-19, changes in healthcare access, or the adoption of new treatment guidelines. The findings could provide valuable insights into how a global health crisis influences medication usage and help optimize future healthcare responses, particularly for chronic conditions like diabetes.

METHODS

Study design and data collection

This descriptive analysis was carried out using publicly accessible data from the official website of the Medicines and Medical Devices Agency of Serbia (ALIMS). According to the Law on Medicines and Medical Devices of the Republic of Serbia (RS), the ALIMS is in charge of gathering, analyzing, and disseminating statistics on medication use annually at the national level. To understand pharmaco-economic and pharmaco-epidemiological indicators, data are gathered using the World Health Organization's (WHO) methodology for data collection (ALIMS 2020).

Data on antidiabeticdrugs utilization were analyzed from 2006 to 2022, based on the Anatomical Therapeutic Chemical (ATC) Classification System (WHO 2023). Both a classification system and a unit of measurement are necessary for quantifying drug use. For this research, a technical unit of measurement known as the Defined Daily Dose (DDD) was generated to address the criticisms of conventional units of measurement. (WHO 2024). The ATC/DDD system is designed to be a tool for drug use research and monitoring in order to enhance the quality of drug usage (WHO 2024).

Antidiabetic drugs are coded as follows: A10A (insulins and analogues), A10B (blood glucose lowering drugs, excl. insulins), A10X (other drugs used in diabetes) (WHO 2023). The following drugs belong to group A10A: insulins and analogues for injection, fast-acting; insulins and analogues for injection, intermediate-acting; insulins and analogues for injection, intermediate- or long-acting combined with fast-acting; insulins and analogues for injection, long-acting; insulins and analogues for inhalation (WHO 2023). The major classes of oral antidiabeticdrugs (A10B) include biguanides, sulfonylureas, sulfonamides (heterocyclic), combinations of oral blood glucose lowering drugs, alpha glucosidase inhibitors, thiazolidinediones, dipeptidyl peptidase 4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) analogues, sodium-glucose co-transporter 2 (SGLT2) inhibitors, other blood glucose lowering drugs, excl. insulins (WHO 2023, Chaundhury 2017).

The study did not include antidiabetic drugs that were used only during the first few years of the study period, as well as those antidiabetic drugs that were not used during the COVID-19 pandemic (insulin pork (fast-acting), insulinpork (combined), insulin human (long-acting), insulin human (intermediate-acting), gliquidone, glipizide, rosiglitazone, metformin and glibenklamid, alogliptin, exenatid).

Study outcome

The primary study outcome was the DDD per 1,000 individuals for each medication. DDD is the average daily maintenance dose of a medication when used in adults in its main indication (18). Price, strength or package size have no impact on the specified daily dose, which is a technical unit that is the average daily dose of a medication used for its primary indication in humans. For every ATC code and administration method (oral, parenteral, inhalation, etc.), a single DDD is allocated. A rough estimate of the actual drug consumption is provided by drug utilization data displayed as DDDs (ALIMS 2020, WHO 2024).

The value of DDD/1,000 people per day provides an insight into how many residents (out of 1,000) used the observed drug and were exposed to its effects in one day. The number of residents who used the substance during the investigation period was correlated with the data that was gathered. The Republic of Serbia's Statistical Office's official records provided the population size data (ALIMS 2020).

Ethics statement

Publicly accessible data were taken from the ALIMS's official website in order to perform this analysis. There were no human or animal subjects in this study, and participant agreement was not required because secondary aggregated data were used instead. The study was therefore exempt from the Ethics Committee's ethical assessment procedure.

Data analysis

The joinpoint regression analysis (version 4.9.1.0, https://surveillance.cancer.gov/joinpoint/) was applied to investigate the dynamics of antidiabetic drugs utilization. Using the trend data, this approach looks more closely at changes that the traditional linear model would miss. "Joinpoints" are used to indicate trend shifts (increase, decrease) (NCI 2024, CDC 2021). Time (2006–2021) was the independent variable in the joinpoint regression model. For each antidiabetic drug, the dependent variables in this model were DDD/1,000 residents. The error variance was assumed to be constant. The software determines the maximum number of joinpoints. Consequently, a maximum of two join points could be detected during the course of 17 years.

RESULTS

A total of 28 antidiabetic drugs were included in the joinpoint analysis. Jointpoint regression analysis from 2006–2022 observation period showed notable changes in the use of following antidiabetic drugs from 2019 (the cut-off year following the COVID-19 pandemic's announcement):

• GLP-1 analogues:dulaglutide (significant increase starting from 2020);

• Insulins and analogues for injection, long-acting: insulin detemir (significant increase 2006-2013, sharp increase starting from 2013, then sharp decline starting from 2019);

• Insulins and analogues for injection, intermediate- or long-acting combined with fast-acting: insulin lispro (significant increase 2011-2017, sharp decline starting from 2020);

• Insulins and analogues for injection, fast-acting: insulin lispro (significant increase 2011-2020, sharp decline starting from 2020) (Figure 1).

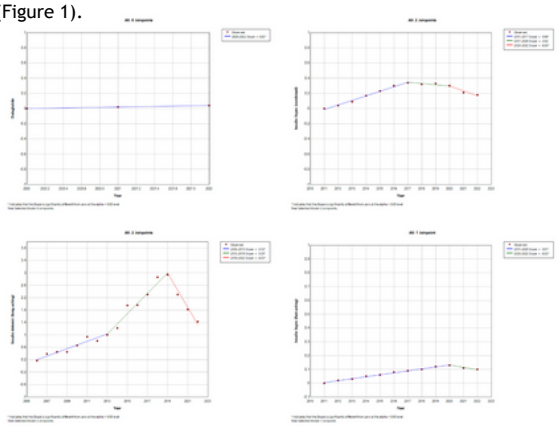


Figure 1.Significant shifts in the antidiabetic consumption during COVID-19 pandemic, joinpoint regression analysis

According to the jointpoint regression analysis, there was a change in the use of certain antidiabetic drugs significantly before the COVID-19 pandemic, specifically:

• Biguanides: metformin (significant increase starting from 2006);

• Sulfonamides: glimepiride (significant increase 2006-2016, sharp decline starting from 2016), glibenclamide (significant increase 2006-2008, sharp decline starting from 2008, slowly increase starting from 2011);

• Combinations of oral blood glucose lowering drugs: metformin and sitagliptin (significant increase starting from 2016) (Figure 2a);

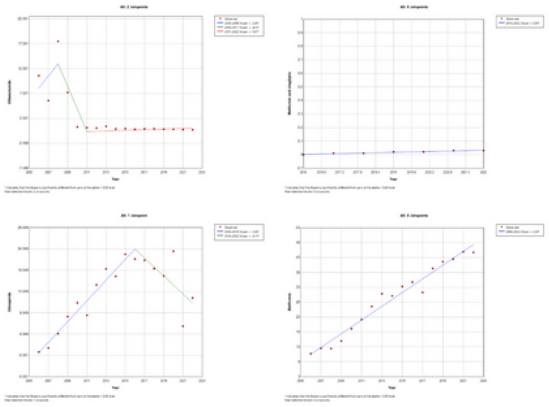


Figure 2a. Significant change in the consumption of oral antidiabetic drugs (biguanides, sulfonamides, combinations of oral blood glucose lowering drugs) before the COVID-19 pandemic, joinpoint regression analysis

• Thiazolidinedione: pioglitazone (significant increase 2013-2015, sharp increase starting from 2015);

• Alpha glucosidase inhibitors: acarbose (significant increase 2006-2012, then decline starrting from 2012)

• DPP-4 inhibitors: sitagliptin (significant increase starting from 2010);

• SGLT-2 inhibitors: empagliflozin (significant increase starting from 2018) (Figure 2b);

• Insulins and analogues for injection, long-acting: insulin degludec (significant increase starting from 2017), insulin glargine (significant increase starting from 2006);

• Insulins and analogues for injection, fast-acting: insulin aspart(significant increase 2006-2014, sharp increase starting from 2014), insulin glulisine (significant increase starting from 2008), insulin human (significant increase starting from 2006);

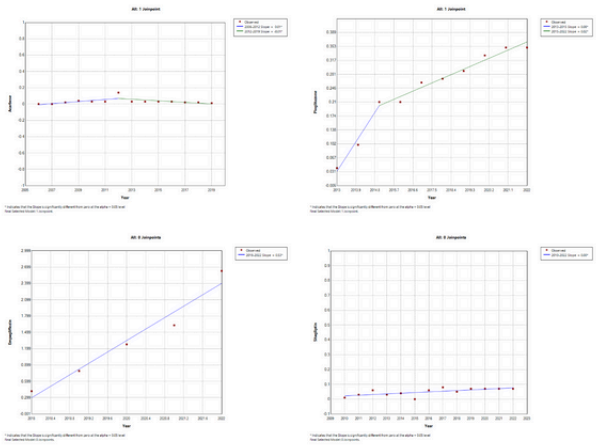


Figure 2b. Significant change in the consumption of oral antidiabetic drugs (thiazolidinedione, alpha glucosidase inhibitors, DPP-4, SGLT-2) before the COVID-19 pandemic, joinpoint regression analysis

• Insulins and analogues for injection, intermediate- or long-acting combined with fast-acting: insulin human (significant decline starting from 2011) (Figure 3);

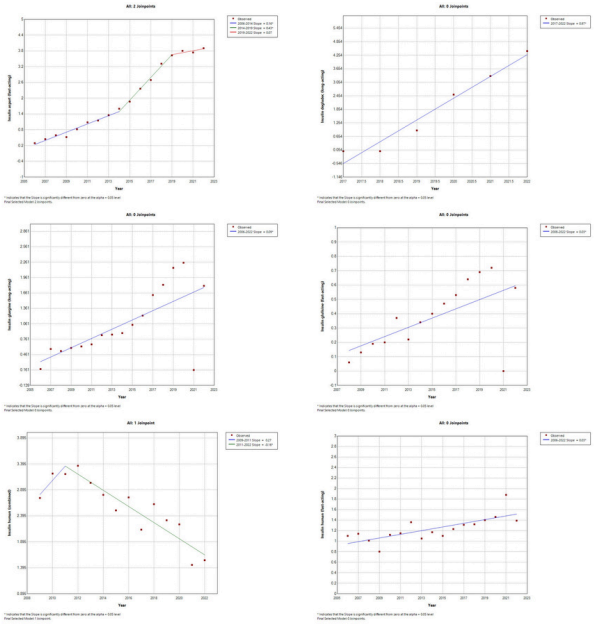


Figure 3. Significant change in the consumption of insulinsbefore the COVID-19 pandemic, joinpoint regression analysis

Other antidiabetics: repaglinide (significant decline 2006-2011, sharp increase starting from 2011, then sharp decline starting from 2017) (Figure 4).

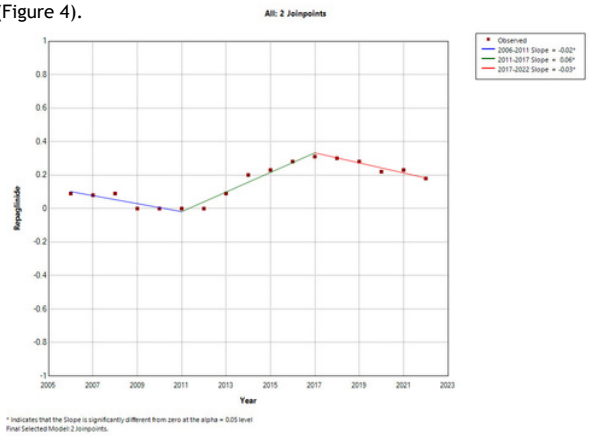
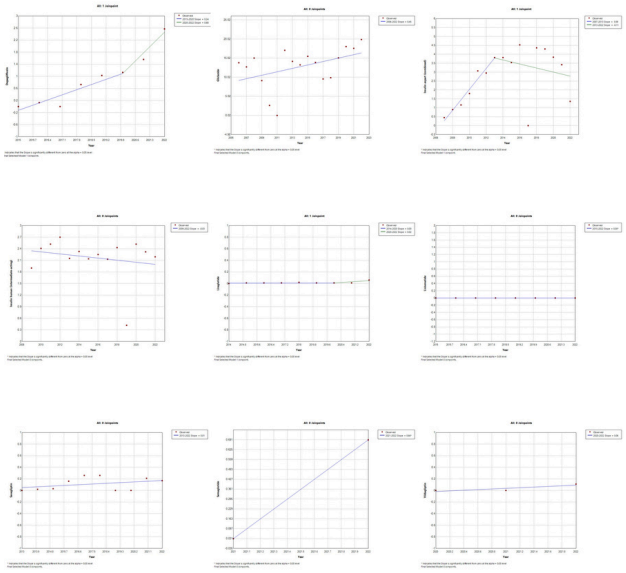


Figure 4.Significant change in the consumption of otherantidiabetic drugs before the COVID-19 pandemic, joinpoint regression analysis

As for other antidiabetic drugs, the joinpoint analysis did not show changes in the consumption (Supplemental figure S1).



Supplemental figure S1. Non significant changes in the consumption of antidiabetic drugs before the COVID-19 pandemic, joinpoint regression analysis

DISCUSSION

This study showed that at the beginning of the COVID-19 pandemic, there was an increase in consumption of dulaglutide and a decrease in consumption of insulin detemir, insulin lispro (combined) and insulin lispro (fast-acting).

Since January 2020, a new coronavirus known as the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused an extraordinary COVID-19 outbreak worldwide. According to data from the first few months of 2020, the majority of COVID-19 patients had pre-existing chronic illnesses, such as diabetes, heart disease, and hypertension being the most common (Yingy et al. 2020). Numerous studies have shown that COVID-19 has more severe clinical presentation in people with diabetes compared to healthy individuals (Cariou et al 2020, Shi et al. 2020, Seiglie et al. 2020). The higher frequency and severity of COVID-19 infection in diabetics can be explained by several factors. Although innate immunity defects that impact phagocytosis, neutrophil chemotaxis, and cell-mediated immunity places people with diabetes at a higher risk of contracting the infection in general, the high incidence of diabetes in severe COVID-19 cases may be a reflection of the higher prevalence of type 2 diabetes in the elderly. Additionally, diabetes later in life is linked to cardiovascular disease, which may help to explain the link between COVID-19 and poor outcomes (Bornstein et al. 2020). Also, the majority of patients with type 2 diabetes are overweight or obese (Singh and Khunti 2022). Since obesity and diabetes are known to contribute to the severity and mortality associated with COVID-19, national guidelines and recommendations have been developed to assist health care workers in adapting patient care to the new challenges posed by the pandemic (Giorgino et al. 2021).

Despite the growing prevalence of diabetes, there are several possible explanations for the increased consumption of a newer antidiabetic drug (dulaglutide) from the group of GLP-1 analogues, as well as the decreased consumption of certain insulin preparations since the beginning of the COVID-19 pandemic in the RS. Moreover, the consumption of newer antidiabetic drugs from the DPP-4 inhibitors and SGLT-2 inhibitors subgroups has significantly increased even before the start of the COVID-19 pandemic. Theoretically, GLP-1 analogues can counteract the heightened inflammatory response brought on by the SARS-CoV-2 infection in the lung, but they cannot actually control the infection itself. The use of newer antidiabetics may delay the initiation of insulin therapy in type 2 diabetes, because the availability of these drug groups provides a wider choice for clinicians before considering insulin therapy (Kostev et al. 2019).

While GLP-1 analogues have positive cardiovascular and renal effects, insulin has a neutral effect in this respect, but has a high risk of hypoglycemia and weight gain (ADA 2023, Davies et al. 2022). In addition, because of their incretineffect and anorexigenic properties, GLP-1 analogues have also been used to treat obesity (Probst et al. 2023). Interest in demand and cost forecasts has increased since the Food and Drug Administration (FDA) approved a number of GLP-1 linked to notable weight loss (Wright et al 2023). It is therefore not surprising that since 2022, a shortage of medicines containing glucagon peptide-1 (GLP-1) receptor agonists has been registered in EU member states as a result of increased demand for these medicines (treatment of diabetes and obesity) in combination with other causes such as production capacity constraints (EMA 2024).

Continuous glucose monitoring lowers the risks of hypoglycemia linked to insulin therapy, and insulin has been used extensively for decades in critically ill hospitalized patients with diabetes mellitus (Lu et al. 2018). The results of this research showed that the consumption of fast-acting and long-acting insulin started to increase statistically significantly mainly since 2006, while the use of combined insulin (intermediate- or long-acting with fast-acting) decreased significantly since 2011. Interestingly, during the COVID-19 pandemic, insulin was also a favored course of treatment for severely ill diabetes patients (Grupta et al. 2020). Many people with diabetes may have experienced impaired glycemic control as a result of stress associated with the pandemic, lifestyle changes (such as increased sedentary behavior, dietary alterations, and decreased physical activity), and disruption of health care delivery (Bharill et al. 2022). In a study investigating trends and regional differences in the use of antidiabetic drugs between 2015 and 2021 in Hungary, the overall use of antidiabetic drugs reaches an interesting peak in 2020. This utilization peak coincided with the COVID -19 outbreak when the Hungarian population tended to stock their chronic medications, which reflected a combination of fear, precautionary behavior, and the desire for continuity in managing a chronic health condition amid the global health crisis (Csatordai et al. 2024).

Regarding other antidiabetic drugs subgroups, our results showed that metformin use has increased significantly since 2006, and has continued this trend until 2022. A high metformin use was similarly observed in Hungary, where metformin was the most commonly used antidiabetic drug alone or in fixed-combination with other antidiabetic drugs, and in Denmark, where metformin use was 39% of the total antidiabetic drugs use in 2021 (Csatordai et al. 2024, Pottegard et al. 2023). Sulfonylureas are still included in international therapeutic guidelines, although this group of antidiabetic drugs is well-known for its side effects, such as hypoglycemia and weight gain, and also does not reduce the risk of major cardiovascular events. The utilization of sulfonylureas has shown high differences between the individual preparations in this study. Although the use of glimepiride and glibenclamide began to increase from 2006 until 2011, after which their use began to decrease except for glibenclamide whose utilization continues to increase significantly. Differences in antidiabetic drugs use are also noted among some European countries. In Denmark, the use of sulfonylurea was very low at about 3.6% in 2021, while in Romania it was estimated at 27.9% of the total consumption of antidiabetic drugs in 2019 (Pottegard et al. 2023, Bucsa et al. 2021). Comparing the results of a previously study in Hungary (Csatordai et al. 2024), to the results of our study, it was revealed that use of alpha glucosidase inhibitors and glinides constantly decreased, while the use of thiazolidinediones increased significantly since 2013, with a sharp rise since 2015 only in Serbia.

This study strength is the opportunity to have complete data gathered from ALIMS official website, which suggests that the findings are generalizable to the entire population. Every year, the ALIMS, submits a report on the sales and usage of pharmaceuticals. Therefore, the term "drug consumption" in this context refers to the use of medications, in this case antidiabetics, by all citizens of the RS, without considering the reasons for use, duration of treatment, or other particular information pertaining to the patient or the facility where the patient received treatment. As a result, our ability to conduct further analyses regarding the indications in which specific antidiabetics were most commonly used to perhaps connect them to the COVID-19 pandemic was restricted. Also, we were unable to stratify antidiabetic drugs for type 1 and type 2 DM. We made an effort to outline and talk about a few possible explanations for the rise and fall in the usage of the various antidiabetics prior to and during the epidemic. However, as there are many possible causes for these shifts, more qualitative research in clinical settings across the nation is required to fully comprehend the real causes.

CONCLUSION

The relationship between COVID-19 and antidiabetic drugs has been a topic of much interest since the pandemic began, especially because diabetes is one of the most common pre-exsisting chronic illnesses associated with severe COVID-19 outcomes. Our study showed that at the beginning of the COVID-19 pandemic, there was an increased consumption of dulaglutide and a declined consumption of insulin detemir, insulin lispro (combined) and insulin lispro (fast-acting). For people with diabetes, taking antidiabetic drugs during the COVID-19 pandemic was critical since stable blood sugar levels lower the likelihood of serious consequences from the virus. This analysis showed that diabetes treatment is changing with the rise of COVID-19. The diabetes treatment should be optimized to provide the best possible care. Therefore, the use of antidiabetic drugs in the context of COVID-19 requires careful consideration.

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