University of Szeged

Faculty of Pharmacy

Doctoral School of Pharmaceutical Sciences

Institute of Clinical Pharmacy

UTILIZATION OF ANTIDIABETIC MEDICATIONS IN HUNGARY BETWEEN 2008 AND 2021, FOCUSING ON NOVEL ANTIDIABETIC DRUGS

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Dr. Márta Csatordai

Supervisor:

Dr. Péter Doró

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ABBREVIATIONS

ATC	anatomic therapeutic chemical classification
DDD	defined daily dose
DDD/TID	defined daily dose per 1000 inhabitants per day
DPP4I	dipeptidyl peptidase-4 inhibitor
GLP1A	glucagon-like peptide-1 analogue
HbA1c	glycated hemoglobin A1c
IDF	International Diabetes Federation
NHIF	National Health Insurance Fund
SGLT2I	sodium-glucose co-transporter-2 inhibitor
WHO	World Health Organization

1. INTRODUCTION

1.1. Diabetes and therapy

Diabetes is a chronic disease affecting an increasing number of people worldwide. The global prevalence of diabetes has almost doubled over the last 30-40 years (4.7% in 1980 and 8.5% in 2014 among the adult population) [1]. According to the International Diabetes Federation Diabetes Atlas 2021, 537 million adults aged 20 to 79 years (10.5% of this population) have diabetes worldwide, and by 2045, this number will reach 783 million (12.2%) [2]. In Hungary, 14.2% of adults (aged 19 years and older) registered with general practitioners had diabetes in 2021, according to the database of the Hungarian Central Statistical Office [3].

Uncontrolled or poorly controlled diabetes has serious consequences such as increased risk of heart attack, stroke, kidney failure, leg amputation, vision loss, and nerve damage [1]. It is estimated that nearly 6.7 million adults between the ages of 20 and 79 years died from diabetes or its complications in 2021 [2]. Additionally, the disease puts high financial pressure on both patients and the healthcare system. Although the estimates are different, it has been shown that the global cost of diabetes can be enormous. It is estimated that the total cost of diabetes (direct and indirect) was 1.31 trillion USD worldwide, which was 1.8% of the global GDP in 2015 [4]. The IDF Diabetes Atlas emphasizes that the economic burden of diabetes is increasing significantly, and projections show that the direct cost of diabetes can reach 1.03 trillion USD by 2030 [2].

As the global burden of diabetes has increased, diabetes management has received growing attention and has led to intensive pharmacological research. According to therapeutic recommendations, lifestyle changes (including nutrition therapy, physical activity and smoking cessation) and education are essential for type 2 diabetes management, alongside optimal pharmacotherapy [5]. While for type 1 diabetes insulin preparations play a fundamental role in pharmacotherapy, pharmacologic treatment options and therapeutic approaches for type 2 diabetes are more diverse and have changed considerably in recent decades [6]. Novel drug groups, namely dipeptidyl peptidase 4 inhibitors (DPP4Is), glucagon-like peptide-1 analogues (GLP1As) and sodium-glucose co-transporter 2 inhibitors (SGLT2Is), were developed and included in the therapeutic guidelines and received reimbursement from the National Health Insurance Fund [6-8]. Although metformin remains the first choice in the treatment of type 2 diabetes, GLP1As and SGLT2Is have become preferred agents in adults with type 2 diabetes with an established/high risk of atherosclerotic

cardiovascular disease or chronic kidney disease [6, 9-11]. According to the American Diabetes Association-European Association for the Study of Diabetes Consensus Report, diabetes therapy should be individualized, and clinicians should consider patient-specific factors and social determinants that affect treatment choice, such as impact on weight, cardiorenal protection, side effects (e.g., hypoglycemia), complexity of the regimen, cost and availability of medication, age, education, and mental status [12]. Taking into consideration the variety of these factors, the regional differences in diabetes prevalence, and the high number of antidiabetic medications, antidiabetic therapy may vary over a wide range, both at the patient and regional levels. These differences can be quantitative and qualitative.

Previously published data on the utilization of antidiabetic medicines in Italy and Portugal have revealed substantial regional differences [13,14]. Regional differences in medication use can be associated with several factors. Beyond the previously mentioned patient-specific factors, social determinants, disease prevalence, regional differences in health policies, differences in accessibility to healthcare, and the characteristics of prescribing doctors may also influence regional differences [15]. Identifying regional differences in the utilization of medicines can be useful for developing national action plans to improve treatment strategies, optimize the allocation of healthcare resources, and consequently improve the health outcomes of diabetic patients.

Although studies on antidiabetic drug utilization changes have been conducted in Hungary and several other countries, in recent years, the use of novel antidiabetic drug groups specifically has not yet been analyzed in detail in Hungary [16-18]. In addition, previous studies have investigated reimbursed antidiabetic drug utilization in Hungary both at the national and patient levels, while complete utilization (including both reimbursed and non-reimbursed medications) of this medication group and regional utilization differences and their possible determinants have not yet been investigated [19]. This dissertation aims to fills this research gap.

1.2. Importance of drug utilization studies

In 1977 the WHO defined drug utilization as “drug utilization is the marketing, distribution, prescription, and use of drugs in a society, with special emphasis on the resulting medical, social and economic consequences” [20].

In 2005, a more accurate description was defined by the EuroDURG special interest group: “drug utilization research is an eclectic collection of descriptive and analytical methods and

theories for the quantification, the understanding and the evaluation of the processes of prescribing, dispensing and consumption of medicines, and for the testing of interventions to enhance the quality of these processes" [21].

Drug utilization studies are essential for evaluating the trends and changes in medication use. They also provide an opportunity to explore how the availability of new drug groups may reshape prescribing patterns in certain health conditions. In addition, these studies focus not only on medical consequences but also on social and economic aspects [22].

Drug utilization studies can analyze different datasets, the characteristics of the data source are fundamental, and the researcher must consider their strengths and limitations. The source of data in drug utilization studies can be primary or secondary. Primary data are the original data, which are collected directly for the purposes of the research. These data sources can be, for example, interviews using structured questionnaires or data gathered with structured forms from electronic health records or pharmacy dispensing databases. Primary data often provides detailed patient-level data. Secondary data sources are collected for administrative purposes during patient care rather than for answering specific research questions. Secondary data sources can be, for example, wholesale or insurance databases. These databases usually contain aggregate- and population-level data. While the insurance database may provide dispensing information only about reimbursed medications, the wholesale database covers the dispensing data for both reimbursed and non-reimbursed medications [22]. In drug utilization analysis, considerable differences can occur in the same drug group depending on the data source. During the presentation of utilization research, the results must be put into context and the strengths and limitations of the data source must be emphasized. To obtain a more accurate picture of drug consumption in a given country, it may be necessary to analyze several databases.

2. MAIN RESEARCH OBJECTIVES

The aim of this dissertation is to provide a detailed picture of antidiabetic utilization patterns in Hungary, covering a 14-year period, using different data sources.

1) The analysis using the National Health Insurance Fund database aims:
   a) to analyze the utilization changes of antidiabetic medications focusing on the consumption changes of novel antidiabetic drug groups between 2008 and 2017
   b) to explore the financial burden generated by these products between 2008 and 2017.
2) The analysis using wholesale database aims:
   a) to assess the utilization tendencies and regional differences in antidiabetic medication consumption between 2015 and 2021
   b) to identify the possible determinants of regional differences in antidiabetic medication use.

3. METHODS

3.1. Analysis using the National Health Insurance Fund database

3.1.1. Data source

The data were obtained from the medication dispensing database of the Hungarian National Health Insurance Fund (NHIF), the sole and mandatory health insurance provider in Hungary [8]. The NHIF database contains monthly aggregated utilization data on each reimbursed medication for the entire population of Hungary from the ambulatory sector (nearly 10 million people): name of drug, strength, package size, Anatomical Therapeutic Chemical Classification (ATC) code, active ingredient, reimbursement category, number of boxes, total retail cost, total reimbursement cost and total co-payment. In the case of reimbursed medication, the total retail cost is shared between the National Health Insurance Fund (reimbursement cost) and patients (co-payment). The data were aggregated and anonymous; therefore, ethical approval for the study was not required.

Retrospective analysis on drug utilization was conducted covering the period between 2008 and 2017.

3.1.2. Data processing and statistical analysis

The data were analyzed using the WHO's ATC/DDD system (version 2018) and were expressed in Defined Daily Dose per 1,000 inhabitants per day (DDD/TID) [23]. DDD is the assumed average maintenance daily dose of the medication used for its main therapeutic indication in adults, and DDD/TID is calculated using the following formula:

DDD/TID = (amount used in 1 year (mg) x 1,000) / (WHO DDD (mg) x population x 365) [24].

Using the DDD/TID technical unit enables researchers to express the use of drugs in a standardized manner and makes it possible to compare medication use across populations of different sizes. DDD/TID may also provide a rough estimation of the proportion of the population using certain medications. For example, 10 DDD/TID can be interpreted as, on average, 1 per cent of the population using the medication every day [24].

In this study, we analyzed drugs used for diabetes (ATC code: A10) with special emphasis on novel antidiabetic drug groups. Regarding these novel antidiabetic drug groups, medications

with the following ATC codes were included: A10BH and A10BD07-13 for DPP4Is; A10BJ, A10AE54 and A10AE56 for GLP1As; A10BK, A10BD15 and A10BD20 for SGLT2Is.

Descriptive statistics were used to describe the sum of yearly medication use, and relative use was expressed as the proportion of total antidiabetic drug use. Linear regression was applied to analyze trends in the consumption of antidiabetic drug groups in cases where data of minimum five years were available. Trends were described by the regression coefficient (average annual change) and significance (p value) of the regression coefficient. $p<0.05$ was considered as statistically significant.

Microsoft Access and Microsoft Excel (Microsoft Office 2010, Microsoft Corporation, Redmond, WA) and R (version 3.6.0, R Foundation for Statistical Computing Vienna, Austria) programs were used for data analysis.

3.2. Analysis using wholesale database

3.2.1. Data source

For this retrospective drug utilization study, yearly wholesale data on antidiabetic drugs were kindly provided by IQVIA for each Hungarian county (19 counties and capital, covering the total Hungarian population of nearly 10 million people) for the period between 2015 and 2021. IQVIA is a multinational company that provides clinical research services for life science research, including data on drug utilization. The database covers total ambulatory drug sales in Hungary, including both reimbursed and non-reimbursed medications. The dataset contains aggregated sales data at the product level: year, region where the drug was purchased, anatomical therapeutic chemical classification code (ATC) of the active ingredient, name of the product, number of boxes, and number of defined daily doses (DDDs) of each product per year per county.

3.2.2. Data processing and statistical analysis

Data were analyzed using the WHO's ATC/DDD system (version 2022), and the filtered ATC code was A10, which is drugs used in diabetes. Regional consumption data were expressed as defined daily dose per 1000 inhabitants per day (DDD/TID), and relative use was expressed as the percentage of total antidiabetic medication use [24,25].

To show the extent of regional utilization differences, the ratio of the highest and lowest utilization values among the counties was calculated (max/min ratio). To analyze time trends in the use of antidiabetic drug groups, simple linear regression was applied and described with

the regression coefficient and significance (p value) of the coefficient. Statistical significance was set at $p < 0.05$. The dependent variable was the use of antidiabetic drug groups (expressed as DDD/TID), and the independent variable was time (years). The regression coefficient describes trends and shows the average annual changes, while positive coefficients indicate increasing trends, and negative coefficients indicate decreasing trends.

To assess the potential reasons for regional differences in antidiabetic drug use, we analyzed the associations between regional drug utilization data for the year 2021 and possible determinants. Demographic data and possible determinants of antidiabetic drug use were extracted from the Hungarian Central Statistical Office database and the National Health Insurance Fund of Hungary report on the World Diabetes Day if relevant regional data were available [26,27]. These extracted determinants were as follows: unemployment rate, number of public medical card holders per ten thousand inhabitants (type of financial support to reduce medical expenses for socially disadvantaged people as they can obtain specific medicine free of charge up to a monthly maximum limit), regional prevalence of diabetes, percentage of the 60 years and older among the total population, and number of attendances in diabetologic outpatient services (diabetologists) per thousand inhabitants.

Correlations were assessed using the Spearman's rank test. Microsoft Excel (Microsoft Office, 2010, Microsoft Corp., Redmond, WA, USA), R (version 3.6.0, R Foundation for Statistical Computing Vienna, Austria) and Datawrapper (Datawrapper GmbH, Berlin, Germany) were used for data analysis and plotting.

Ethical approval for this study was not required because wholesale drug utilization data were aggregated and not linked to any patient data.

3.3. Further technical considerations

3.3.1. Reimbursement system in Hungary

Regarding the reimbursement system in Hungary, the National Health Insurance Fund is the sole mandatory national health insurance company. GPs can prescribe all antidiabetic medications, but in the case of insulins, GLP1As, SGLT2Is and DPP4Is for the reimbursement, regular diabetologist recommendations and follow-ups are necessary [28].

3.3.2. Handling combination products during the analysis

In drug utilization studies, dealing with combination products can be challenging and handling these data require careful consideration (Table 1). Data regarding the overall use of an active ingredient could be analyzed separately for monocomponent products and combination products, or could be merged together, and analyzed together. When we analyzed the use of each pharmacological class we chose to merge together the use of monocompontent products and combination products, as this method provides results for the overall use of each active ingredient and pharmacological class. However, when we calculated the overall use of antidiabetic medication, we included combination products only once, avoiding the addition of the same product twice.

Insulin and combinations	**Sulfonylureas combinations**	**Metformin combinations**
Insulin glargine and lixisenatid Insulin degludec and liraglutide	Glimepirid and rosiglitazone	Metformin and rosiglitazone Metformin and pioglitazone Metformin and sitagliptin Metformin and vildagliptin Metformin and saxagliptin Metformin and linagliptin Metformin and alogliptin Metformin and dapagliflozin Metformin and empagliflozin Metformin and ertugliflozin
DPP4Is combinations	**GLP1As combinations**	**SGLT2Is combinations**
Metformin and sitagliptin Metformin and vildagliptin Pioglitazone and alogliptin Metformin and saxagliptin Metformin and linagliptin Metformin and alogliptin Sitagliptin and ertugliflozin	Insulin glargine and lixisenatid Insulin degludec and liraglutide	Metformin and dapagliflozin Metformin and empagliflozin Metformin and ertugliflozin Sitagliptin and ertugliflozin

Table 1. Available fixed-dose combinations (pharmacological class and name of active ingredients) in Hungary during the study period (2008-2021)

4. RESULTS

4.1. Analysis using the National Health Insurance Fund database

4.1.1. Utilization trends of antidiabetic drugs

During the ten-year study period (2008-2017), the consumption of antidiabetic drugs showed an 18% increase and reached 74.7 DDD/TID, although in 2015, there was a drop in the total antidiabetic medication use (Table 2). Total insulin use rose by 41%, resulting in 26.4 DDD/TID in 2017. Sulfonylureas were used most frequently in 2008, but from 2009 their use decreased consistently, with a 25% decrease by 2017. The consumption of biguanides as monocomponent preparations fluctuated; after a considerable increase, there was a rapid decrease in 2015. In the following years, consumption slightly increased again, and in 2017, biguanide use was 13.9 DDD/TID. Metformin fixed-dose combination products began to play an increasing role and reached 6.9 DDD/TID by 2017. Alpha glucosidase inhibitors, thiazolidinediones and meglinides were less commonly used and their consumption steadily decreased over the study period (Table 2).

Table 2. Utilization of reimbursed antidiabetic drugs in Hungary between 2008 and 2017 shown in defined daily dose per thousand inhabitants per day (DDD/TID)

ATC code		2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	regression coefficient (95% CI)
		DDD/TID										
A10AB-A10AE06	Insulins	18.76	20.24	21.67	22.74	23.41	24.07	24.85	25.39	25.79	25.86	0.78 (0.62 – 0.94)*
A10AE54, 56	Insulin+GLP1As									0.27	0.54	
A10BA	Biguanides	10.51	12.88	15.07	17.35	18.71	19.98	18.78	11.76	13.15	13.92	0.13 (-0.75 – 1.01)
A10BB	Sulfonylureas	29.18	30.31	29.82	29.41	28.22	27.69	26.42	25.24	24.05	22.73	-0.81 (-1.04 – -0.59)*
A10BD	Combinations of oral blood glucose lowering drugs	1.91	2.19	2.80	3.09	3.44	4.01	4.61	5.11	5.91	6.92	0.53 (0.46 – 0.6)*
A10BD03, 05	Metformin+thiazolidinediones	1.87	1.74	1.50	0.72	0.44	0.36	0.29	0.24	0.21	0.17	-0.2 (-0.28 – -0.13)*
A10BD04	Sulfonylureas+thiazolidinediones	0.04	0.05	0.04	<0.01							
A10BD07, 08, 10, 11, 13	Metformin+DPP4Is	0.01	0.40	1.26	2.37	3.00	3.65	4.32	4.85	5.22	5.50	0.65 (0.57 – 0.73)*
A10BD09	Thiazolidinediones+DPP4Is								<0.01	0.01	0.01	
A10BD15, 20	Metformin+SGLT2Is								0.02	0.48	1.23	
A10BF	Alpha glucosidase inhibitors	2.54	1.41	1.13	0.92	0.72	0.62	0.53	0.46	0.38	0.31	-0.19 (-0.28 – -0.1)*
A10BG	Thiazolidinediones	0.15	0.22	0.22	0.18	0.12	0.11	0.10	0.09	0.07	0.07	-0.02 (-0.02 – -0.01)*
A10BH	Dipeptidyl peptidase 4 inhibitors	0.04	0.31	0.50	0.81	1.02	1.26	1.38	1.56	1.74	1.91	0.21 (0.19 – 0.22)*
A10BJ	Glucagon-like peptide-1 receptor agonists			0.06	0.20	0.24	0.35	0.63	0.86	0.86	0.94	0.14 (0.11 – 0.17)*
A10BK	Sodium-glucose co-transporter 2 inhibitors							0.02	0.39	0.97	1.52	
A10BX02, 03	Meglinides	0.09	0.07	0.06	0.05	0.04	0.03	0.03	0.02	0.02	0.02	-0.01 (-0.01 – -0.01)*
	Total novel antidiabetic drug use	**0.04**	**0.71**	**1.82**	**3.38**	**4.26**	**5.26**	**6.35**	**7.68**	**9.56**	**11.66**	**1.25 (1.11 – 1.38)***
	Total antidiabetic drug use	**63.18**	**67.63**	**71.34**	**74.75**	**75.93**	**78.12**	**77.35**	**70.87**	**73.23**	**74.73**	**0.91 (-0.08 – 1.91)**

GLP1A- Glucagon-like peptide-1 receptor agonists; DPP4I- Dipeptidyl peptidase 4 inhibitors; SGLT2I- Sodium-glucose co-transporter 2 inhibitors; novel antidiabetic drugs include GLP1As, DPP4Is and SGLT2Is; *P<0.05; regression coefficient describes trends showing the average annual changes

4.1.2. Utilization trends of novel antidiabetic drugs

From 2008, total novel antidiabetic drug use increased constantly and significantly, from 0.04 DDD/TID to 11.7 DDD/TID, which was the largest increase among all antidiabetic drug groups during the study period (Table 2). The share of novel antidiabetic drugs rose to 16% of the total antidiabetic medication use by 2017 (Table 3).

During the study period, the most widely used novel antidiabetic drug group were the DPP4Is, which first appeared on the Hungarian market in 2008. Their consumption showed a dynamic growth and reached 7.4 DDD/TID in 2017 (Table 3). The aggregated DPP4I use was 64% of the total novel antidiabetic drug consumption in 2017. While sitagliptin monocomponent products constituted the majority of DPP4I use in 2008, in 2017 three-quarters of the total DPP4I use was fixed-dose preparations with metformin. Regarding fixed-dose combinations, metformin+sitagliptin was used the most frequently in 2017, but metformin+vildagliptin and metformin+linagliptin consumption was also notable. Saxagliptin and alogliptin and their fixed-dose combinations with metformin were rarely used and until 2017 its utilization was decreased (Table 3).

Among the novel antidiabetic drugs, GLP1As accounted for the lowest utilization rates, although they did show an increase in use over time. GLP1As first appeared in the NHIF database in 2010 and by 2017 their use was 1.5 DDD/TID, 13% of the total novel antidiabetic drug consumption. Fixed-ratio combinations (mainly insulin degludec+liraglutide and less often insulin glargine+lixisenatide) shared one-third of the total GLP1A consumption while monocomponent medications represented two-thirds of GLP1A utilization in 2017. The most commonly used monocomponent product in 2017 was liraglutide, followed by dulaglutide, lixisenatide and exenatide (Table 3).

Although SGLT2Is first appeared in the utilization data only in 2014, their total consumption grew to 2.8 DDD/TID during the subsequent 4-year period and accounted for 24% of the total novel antidiabetic drug use in 2017. The utilization of monocomponent SGLT2I preparations increased dynamically and reached 1.5 DDD/TID, while the use of SGLT2I+metformin was slightly lower in 2017. Approximately two-thirds of the total SGLT2I utilization was empagliflozin and its combinations (Table 3).

Table 3. Utilization of novel antidiabetic drugs between 2008 and 2017 in Hungary shown in defined daily dose per thousand inhabitants per day (DDD/TID)

ATC code		2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
						DDD/TID					
	DPP4Is total	**0.04**	**0.71**	**1.76**	**3.18**	**4.02**	**4.91**	**5.70**	**6.41**	**6.98**	**7.42**
A10BH01	sitagliptin	0.04	0.26	0.33	0.44	0.53	0.59	0.67	0.72	0.82	0.93
A10BH02	vildagliptin	<0.01	0.05	0.11	0.15	0.18	0.22	0.26	0.31	0.34	0.35
A10BH03	saxagliptin			0.06	0.22	0.24	0.21	0.17	0.14	0.11	0.09
A10BH04	alogliptin							<0.01	0.03	0.03	0.02
A10BH05	linagliptin					0.07	0.24	0.29	0.37	0.45	0.53
A10BD07	metformin+sitagliptin		0.15	0.60	1.28	1.72	2.09	2.33	2.52	2.75	3.03
A10BD08	metformin+vildagliptin	<0.01	0.25	0.66	1.09	1.28	1.37	1.48	1.67	1.81	1.84
A10BD09	pioglitazon+alogliptin								<0.01	0.01	0.01
A10BD10	metformin+saxagliptin						0.04	0.13	0.13	0.10	0.08
A10BD11	metformin+linagliptin						0.16	0.38	0.48	0.50	0.49
A10BD13	metformin+alogliptin							<0.01	0.05	0.06	0.05
	GLP1As total			**0.06**	**0.20**	**0.24**	**0.35**	**0.63**	**0.86**	**1.13**	**1.48**
A10BJ01	exenatide			0.01	0.05	0.08	0.07	0.09	0.09	0.06	0.05
A10BJ02	liraglutide			0.05	0.14	0.16	0.28	0.50	0.67	0.65	0.67
A10BJ03	lixisenatide							0.04	0.11	0.12	0.10
A10BJ05	dulaglutide									0.02	0.12
A10AE54	insulin glargine+lixisenatide										<0.01
A10AE56	insulin degludec+liraglutide									0.27	0.54
	SGLT2Is total							**0.02**	**0.41**	**1.45**	**2.76**
A10BK01	dapagliflozin							0.02	0.23	0.38	0.54
A10BK03	empagliflozin								0.16	0.59	0.99
A10BD15	metformin+dapagliflozin								0.01	0.17	0.43
A10BD20	metformin+empagliflozin								0.01	0.30	0.80
	Total novel antidiabetic drug use (% of total antidiabetic drug use)	**0.04 (0.1)**	**0.71 (1.1)**	**1.82 (2.6)**	**3.38 (4.5)**	**4.26 (5.6)**	**5.26 (6.7)**	**6.35 (8.2)**	**7.68 (11)**	**9.56 (13)**	**11.66 (16)**
	Total antidiabetic drug use	**63.18**	**67.63**	**71.34**	**74.75**	**75.93**	**78.12**	**77.35**	**70.87**	**73.23**	**74.73**

DPP4I - Dipeptidyl peptidase 4 inhibitors; GLP1A- Glucagon-like peptide-1 receptor agonists; SGLT2I- Sodium-glucose co-transporter 2 inhibitors

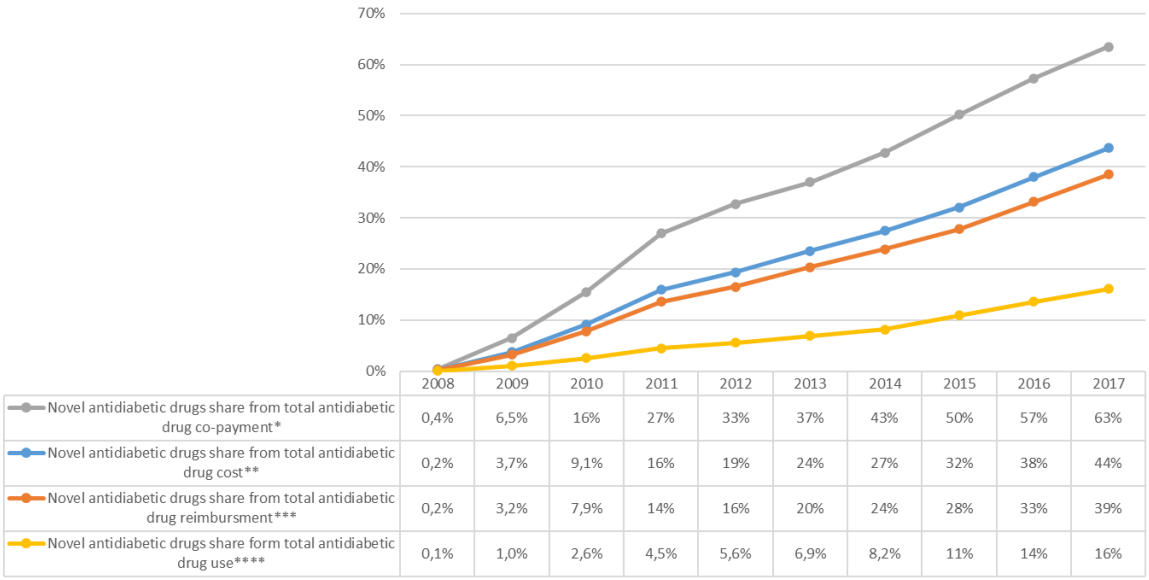
4.1.3. Financial burden of novel antidiabetic drugs

The increased utilization of novel antidiabetic drugs resulted in a higher health care expenditure for both people with diabetes and the NHIF, because these drugs have a considerably higher price than other antidiabetic drugs. Comparing the average retail prices (reimbursement + co-payment) per DDD in 2017, among subcutaneous preparations, GLP1As were approximately 4-5 times more expensive than human insulins. Among oral antidiabetic drugs, DPP4Is cost approximately 12-15 times more than metformin, and SGLT2Is were approximately 15 times more expensive than metformin (Table 4).

The total expense of antidiabetic medications increased by 94% since 2008, reaching 50.04 billion HUF (161.4 million EUR) in 2017. Within total antidiabetic medication expenditure, the share of novel antidiabetic drugs has grown substantially. By 2017, the total cost of novel antidiabetic drug utilization accounted for 44% of the total antidiabetic medication expenditure (Figure 1). As all novel antidiabetic drugs were reimbursed medications, both the health insurance provider's and individuals' expenses on these drugs have risen significantly since 2008, but to a different extent. In 2017, novel antidiabetic drugs had a 39% share of the NHIF's total reimbursement expenditure on antidiabetic drugs, while 63% of the co-payment for antidiabetic drugs was spent on novel antidiabetic drugs (Figure 1).

Table 4. Financial burden of antidiabetic drugs: total average daily cost (reimbursement+co-payment) per active ingredient expressed in HUF
Total average daily cost comes from: total yearly retail cost/total yearly DDD

WHO ATC	ACTIVE INGREDIENT	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
A10AB01	insulin (human)	179	179	179	179	180	182	182	182	182	182
A10AB04	insulin lispro	242	230	230	230	231	234	236	236	236	236
A10AB05	insulin aspart	230	230	230	230	235	236	236	236	236	236
A10AB06	insulin glulisin	247	230	230	230	231	233	233	233	233	233
A10AC01	insulin (human)	179	179	179	179	180	182	181	182	182	182
A10AD01	insulin (human)	175	177	178	179	181	183	183	183	184	184
A10AD04	insulin lispro	249	247	247	247	248	251	253	253	253	253
A10AD05	insulin aspart	247	247	247	247	253	253	253	253	253	253
A10AE04	insulin glargine	414	414	414	414	415	416	416	415	410	406
A10AE05	insulin detemir	414	414	414	415	433	433	433	433	433	433
A10AE06	insulin degludec	-	-	-	-	-	-	-	838	838	838
A10AE54	insulin glargine+lixisenatide	-	-	-	-	-	-	-	-	-	1424
A10AE56	degludek inzulin+liraglutid	-	-	-	-	-	-	-	-	1792	1792
A10BA02	metformin	28	29	30	30	29	29	29	29	29	29
A10BA03	buformin	59	59	59	-	-	-	-	-	-	-
A10BB01	glibenclamid	27	-	-	-	-	-	-	-	-	-
A10BB07	glipizid	56	-	-	-	-	-	-	-	-	-
A10BB08	gliquidon	53	53	53	53	52	52	52	52	52	52
A10BB09	gliclazid	56	44	43	42	41	41	41	41	40	40
A10BB12	glimepirid	31	31	31	30	28	26	25	24	24	24
A10BD03	metformin+roziglitazon	310	320	326	324	-	-	-	-	-	-
A10BD04	glimepirid+roziglitazon	624	647	657	661	-	-	-	-	-	-
A10BD05	metformin+pioglitazon	-	418	418	418	419	421	421	421	421	421
A10BD07	metformin+sitagliptin	-	397	397	397	398	400	400	400	400	400
A10BD08	metformin+vildagliptin	416	416	416	416	417	418	418	418	418	418
A10BD09	pioglitazon+alogliptin	-	-	-	-	-	-	-	442	442	442
A10BD10	metformin+saxagliptin	-	-	-	-	-	428	428	428	428	428
A10BD11	metformin+linagliptin	-	-	-	-	-	418	418	418	418	418
A10BD13	metformin+alogliptin	-	-	-	-	-	-	362	362	362	362
A10BD15	metformin+dapagliflozin	-	-	-	-	-	-	-	453	453	453
A10BD20	empagliflozin+metformin	-	-	-	-	-	-	-	454	454	454
A10BD23	metformin+ertugliflozin	-	-	-	-	-	-	-	-	-	-
A10BD24	sitagliptin+ertugliflozin	-	-	-	-	-	-	-	-	-	-
A10BF01	acarbose	144	139	139	138	134	133	132	131	131	135
A10BG02	rosiglitazon	331	331	331	331	-	-	-	-	-	-
A10BG03	pioglitazon	400	400	400	400	401	403	403	403	403	403
A10BH01	sitagliptine	371	371	371	371	373	375	375	375	375	375
A10BH02	vildagliptin	449	449	449	449	451	453	453	453	453	453
A10BH03	saxagliptin	-	-	399	399	400	402	402	402	402	402
A10BH04	alogliptin	-	-	-	-	-	-	360	361	361	361
A10BH05	linagliptin	-	-	-	-	413	414	414	414	414	414
A10BJ01	exenatide	-	-	801	700	671	667	843	904	921	924
A10BJ02	liraglutide	-	-	1244	1244	1243	1243	1243	1243	1243	1243
A10BJ03	lixisenatide	-	-	-	-	-	-	818	800	802	795
A10BJ05	dulaglutid	-	-	-	-	-	-	-	-	1040	1030
A10BJ06	semaglutide	-	-	-	-	-	-	-	-	-	-
A10BK01	dapagliflozin	-	-	-	-	-	-	428	428	428	428
A10BK03	empagliflozin	-	-	-	-	-	-	-	478	453	435
A10BK04	ertugliflozin	-	-	-	-	-	-	-	-	-	-
A10BX02	repaglinid	126	126	126	126	127	127	127	127	127	127
A10BX03	nateglinid	292	292	292	292	293	296	296	296	296	296



	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
Novel antidiabetic drugs share from total antidiabetic drug co-payment*	0,4%	6,5%	16%	27%	33%	37%	43%	50%	57%	63%
Novel antidiabetic drugs share from total antidiabetic drug cost**	0,2%	3,7%	9,1%	16%	19%	24%	27%	32%	38%	44%
Novel antidiabetic drugs share from total antidiabetic drug reimbursment***	0,2%	3,2%	7,9%	14%	16%	20%	24%	28%	33%	39%
Novel antidiabetic drugs share form total antidiabetic drug use****	0,1%	1,0%	2,6%	4,5%	5,6%	6,9%	8,2%	11%	14%	16%

Figure 1. Financial burden of novel antidiabetic drug groups. The figure compares the relative increase of utilization and the relative increase of expenses (total cost, reimbursement and co-payment) spent on the novel antidiabetic drugs from the total reimbursed antidiabetic drugs

The total cost is shared between the National Health Insurance Fund (reimbursement) and individuals (co-payment).

* Relative increase in individuals' expenses, expressed as the relative share of novel antidiabetic drug co-payment (30% of total price) from the total antidiabetic drug co-payment.

** Relative increase in total drug expenditure (co-payment+reimbursement), expressed as the relative share of novel antidiabetic drug expenditure from the total antidiabetic drug expenditure.

*** Relative increase in the expenditure of the National Health Insurance Fund, expressed as the relative share of novel antidiabetic drug reimbursement (70% of total price) from the total antidiabetic drug reimbursement.

**** Relative increase in the novel antidiabetic drug use (DDD/TID) from the total antidiabetic drug use (DDD/TID).

4.2. Analysis using wholesale database

4.2.1 National and regional antidiabetic drug utilization

During the study period (2015-2021), both national and regional antidiabetic medication use showed a growing tendency, but to different extents. The total national antidiabetic medication use increased by 7.6% and reached 94.8 DDD/TID in 2021; however, in 2020, there was a peak of 97.4 DDD/TID. In most of the counties the rise in total antidiabetic consumption was considerable, between 4.5% and 16.5% over the 7 years, except in the capital (Budapest) and in Győr-Moson-Sopron County. The highest antidiabetic medication utilization in 2021 and the highest increase in use during the study period were observed in Békés County (Table 5). The difference in antidiabetic medication use between counties was relatively stable, the max/min ratio was between 1.37 and 1.41 during the study period and south-southwest counties tended to use more antidiabetics.

Regarding the use of antidiabetic subgroups, large and stable interregional differences were observed. During the study period, both insulin use and interregional differences in insulin use were stable (max/min ratio: 1.65-1.70) without a clear geographical gradient (Table 5). In 2021, insulin use was 23.6-30.5% of the total antidiabetic medication consumption. In contrast to insulin utilization, metformin and sulfonylurea use showed dynamic alterations. The utilization of metformin and its combinations showed an emerging trend in all counties and reached 39.1-47.2% of the total antidiabetic medication use at the end of the study period, indicating that metformin and its combinations were the most frequently used antidiabetic medications (Table 5). The south-southwest counties tended to use more metformin than the northeast counties, but the interregional differences in metformin use were the smallest among all antidiabetic drug groups (max/min ratio: 1.46 in 2021, ranging between 1.46 and 1.52 during the study period). Although sulfonylurea use decreased in all counties during the study period, notable differences were observed in the regional consumption (Table 5, Figure 3.). While the use of sulfonylureas was the lowest in Budapest, with 14.8 DDD/TID in 2021, the use of this drug group was the highest in Békés County, with 30.1 DDD/TID (max/min ratio of 2.03). The relative use of sulfonylureas in different regions was still between 14.8% and 25.8% of the total antidiabetic medication consumption in 2021.

Table 5. National and regional trends in the use of antidiabetic drugs over the 7-year period (between 2015 and 2021)

Group name	Antidiabetics total DDD/TID				Insulins and combinations DDD/TID				Metformin and combinations DDD/TID				Sulfonylureas DDD/TID				DPP4Is and combinations DDD/TID				GLP1As and combinations DDD/TID				SGLT2Is and combinations DDD/TID			
Region/County	2015	2021	coeff.	p	2015	2021	coeff.	p	2015	2021	coeff.	p	2015	2021	coeff.	p	2015	2021	coeff.	p	2015	2021	coeff.	p	2015	2021	coeff.	p
Budapest																												
Budapest	87.0	89.1	0.42	0.128	24.7	22.6	-0.32	0.089	33.9	40.4	1.14	<0.001*	23.8	14.8	-1.46	<0.001*	6.7	7.8	0.23	0.009*	0.9	6.3	0.86	0.001*	0.5	5.7	0.88	<0.001*
Pest																												
Pest	83.4	88.5	1.09	0.018*	24.3	24.6	0.14	0.353	32.6	39.9	1.32	<0.001*	23.3	15.2	-1.30	<0.001*	6.0	8.0	0.40	0.001*	0.7	5.1	0.71	<0.001*	0.2	5.2	1.20	<0.001*
Central Transdanubia																												
Fejer	88.9	98.4	1.72	0.003*	24.6	24.9	0.14	0.549	36.0	46.4	1.73	<0.001*	24.0	15.4	-1.38	<0.001*	7.1	9.0	0.38	0.001*	0.9	5.8	0.82	<0.001*	0.6	8.3	1.31	<0.001*
Komarom-Esztergom	88.6	94.7	1.30	0.009*	26.0	25.2	-0.01	0.936	34.6	43.4	1.54	<0.001*	24.8	18.4	-0.99	<0.001*	5.5	7.0	0.29	<0.001*	0.6	4.0	0.57	<0.001*	0.2	5.8	1.17	<0.001*
Veszprem	86.8	94.9	1.46	0.002*	24.6	25.2	0.14	0.427	35.8	42.5	1.15	<0.001*	22.9	15.6	-1.18	<0.001*	6.0	8.9	0.53	<0.001*	0.5	5.1	0.75	<0.001*	0.6	6.9	1.13	<0.001*
Western Transdanubia																												
Gyor-Moson-Sopron	81.9	82.5	0.18	0.432	20.2	19.5	-0.07	0.504	32.5	38.8	1.07	<0.001*	26.3	17.7	-1.42	<0.001*	5.6	6.9	0.26	0.004*	0.6	3.3	0.44	<0.001*	0.1	5.1	0.87	<0.001*
Vas	98.0	102.2	0.82	0.023*	27.4	24.7	-0.41	0.065	37.8	47.7	1.68	<0.001*	28.4	18.6	-1.60	<0.001*	5.8	8.3	0.47	0.003*	1.1	7.0	1.00	<0.001*	0.3	6.9	1.50	<0.001*
Zala	96.1	111.0	2.83	<0.001*	29.4	30.3	0.33	0.235	32.0	43.4	1.98	<0.001*	29.6	24.2	-0.79	<0.001*	8.6	11.8	0.60	<0.001*	0.5	5.3	0.80	<0.001*	0.6	8.8	1.05	<0.001*
Southern Transdanubia																												
Baranya	100.9	108.9	1.48	0.006*	33.5	29.7	-0.65	0.014*	33.3	45.7	2.11	<0.001*	29.4	21.1	-1.31	<0.001*	7.7	9.2	0.30	0.018*	1.0	6.4	0.90	<0.001*	0.6	8.4	1.33	<0.001*
Somogy	97.7	109.1	2.12	<0.001*	26.9	26.9	0.05	0.772	38.6	49.3	1.89	<0.001*	28.2	20.5	-1.26	<0.001*	7.4	9.1	0.34	0.003*	1.0	6.8	0.98	<0.001*	0.5	8.9	0.83	<0.001*
Tolna	103.1	115.5	2.30	<0.001*	32.6	33.1	0.15	0.407	39.1	52.0	2.26	<0.001*	25.8	17.1	-1.40	<0.001*	8.6	11.1	0.46	0.012*	1.3	7.8	1.09	<0.001*	0.4	9.1	0.92	<0.001*
Northern Hungary																												
Borsod-Abauj-Zemplen	86.8	93.5	1.30	0.004*	26.7	26.1	-0.04	0.811	29.8	39.1	1.61	<0.001*	26.5	20.6	-0.93	<0.001*	5.5	8.1	0.50	<0.001*	0.8	3.8	0.51	<0.001*	0.7	6.9	1.05	<0.001*
Heves	91.2	98.6	1.49	0.006*	27.2	28.5	0.32	0.231	32.1	40.6	1.50	<0.001*	29.0	21.7	-1.11	<0.001*	6.5	8.8	0.48	<0.001*	0.7	3.9	0.53	<0.001*	0.5	6.3	0.97	<0.001*
Nograd	86.1	92.3	1.29	0.006*	23.0	23.3	0.15	0.392	30.5	38.4	1.41	<0.001*	29.4	23.5	-0.99	<0.001*	6.7	9.5	0.55	<0.001*	0.6	2.6	0.32	<0.001*	0.6	7.5	0.99	<0.001*
Northern Great Plain																												
Hajdu-Bihar	81.5	87.5	1.26	0.005*	20.5	20.8	0.11	0.297	32.0	40.1	1.45	<0.001*	26.6	19.4	-1.06	<0.001*	6.4	8.9	0.47	<0.001*	0.5	3.9	0.57	<0.001*	0.3	6.8	1.08	<0.001*
Jasz-Nagykun-Szolnok	94.3	104.5	2.16	0.003*	30.5	31.7	0.32	0.077	31.0	40.7	1.72	<0.001*	28.2	21.9	-0.84	0.004*	7.4	10.0	0.49	<0.001*	0.7	3.6	0.49	<0.001*	0.3	7.1	1.08	<0.001*
Szabolcs-Szatmar-Bereg	75.4	83.6	1.70	0.002*	25.8	25.5	0.10	0.565	25.6	35.6	1.72	<0.001*	21.5	15.0	-0.98	<0.001*	5.4	7.9	0.49	<0.001*	0.6	4.0	0.57	<0.001*	0.3	5.6	1.45	<0.001*
Southern Great Plain																												
Bacs-Kiskun	90.1	99.6	1.88	<0.001*	25.6	25.7	0.04	0.814	34.6	44.4	1.74	<0.001*	25.8	19.6	-0.80	0.007*	8.4	10.9	0.43	<0.001*	0.7	3.7	0.51	<0.001*	0.5	9.1	1.49	<0.001*
Bekes	100.2	116.7	3.24	<0.001*	29.4	30.0	0.16	0.422	32.6	45.7	2.32	<0.001*	33.8	30.1	-0.28	0,333	7.7	9.7	0.37	<0.001*	0.5	3.5	0.48	<0.001*	0.5	9.8	1.57	<0.001*
Csongrad-Csanad	84.6	94.5	2.49	0.009*	24.6	23.4	-0.14	0.296	30.4	42.8	2.38	<0.001*	26.4	18.7	-0.79	0,105	5.2	8.1	0.52	<0.001*	0.7	4.4	0.60	<0.001*	0.7	8.5	1.33	<0.001*
Hungary	88.1	94.8	1.35	0.004*	25.7	25.1	-0.03	0.858	32.9	41.8	1.56	<0.001*	25.7	18.2	-1.16	<0.001*	6.6	8.6	0.39	0.001*	0.7	4.9	0.69	<0.001*	0.4	6.8	1.37	<0.001*

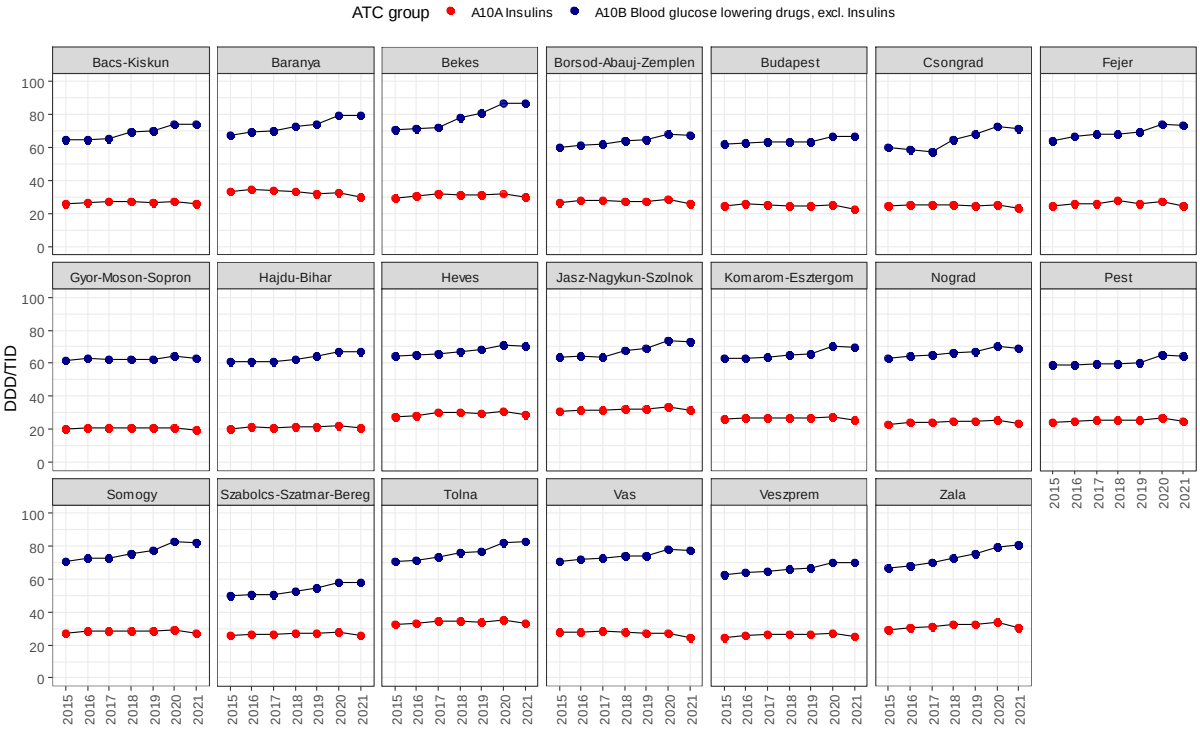
Table shows drug utilization data (expressed in DDD/TID) in the beginning year (2015) and in the ending year (2021). Regarding utilization trends, regression coefficient describes trends showing the average annual changes, the positive coefficient means increasing, negative coefficient means decreasing tendency.

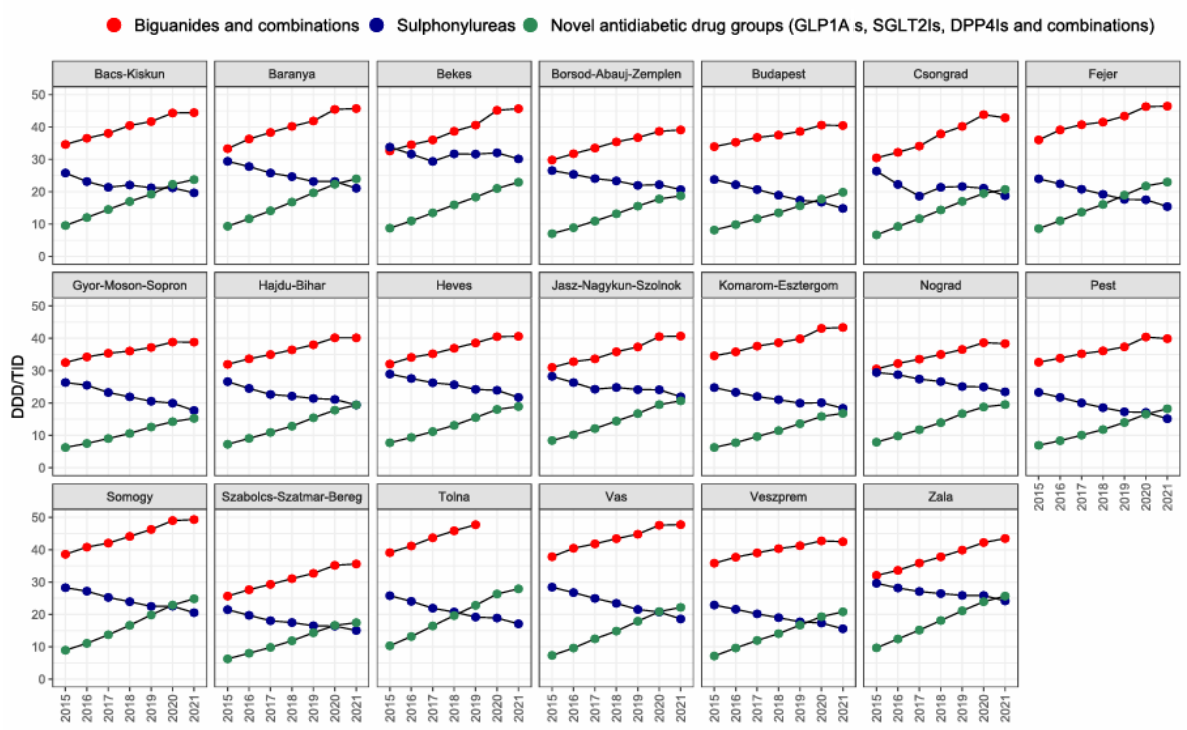
DDD/TID: Defined daily dose per 1000 inhabitants per day; coeff.: regression coefficient; GLP1A: GLP-1 analogues; DPP4I: DPP-4 inhibitors; SGLT2I: SGLT-2 inhibitors; *p<0.05

The use of novel antidiabetic drug groups, namely, DPP4Is, SGLT2Is and GLP1As and their combinations, showed an emerging tendency. The use of DPP4Is was the highest among these drug groups, but after dynamic growth between 2015 and 2020, its use decreased slightly, and in some counties, SGLT2I utilization exceeded DPP4I use by 2021 (Table 5, Figure 2). DPP4Is, SGLT2Is, GLP1As, and their combinations accounted for 19.2-24.1% of the total use of antidiabetic drugs in Hungary in 2021. Regarding interregional differences, GLP1A use showed the highest difference among the antidiabetic drug groups in 2021 (max/min ratio: 3.00). GLP1A utilization was highest in the western regions, mainly in the southwest (Southern Transdanubia), whereas utilization was much lower in the east, mainly in the northern regions of Hungary and the Northern Great Plain (Table 5, Figure 3). SGLT2I use tended to be higher in the southern counties, while in the northern counties, the utilization was much lower, with a max/min ratio of 1.92 in 2021 (Table 5, Figure 3). In the case of DPP4Is, the difference between the regions was lower than that of the other two drug groups; the max/min ratio was 1.70 in 2021, and a clear geographical gradient was not observed.

The utilization of these antidiabetic subgroups expressed in DDD/TID is summarized in Table 5, and the regional utilization tendencies of the different antidiabetic groups are shown in Figure 2. The changes in regional differences in the utilization of antidiabetic drug groups between 2015 and 2021 are shown in Figure 4.

Figure 2. Utilization tendencies of antidiabetic medication in Hungarian counties between 2015 and 2021





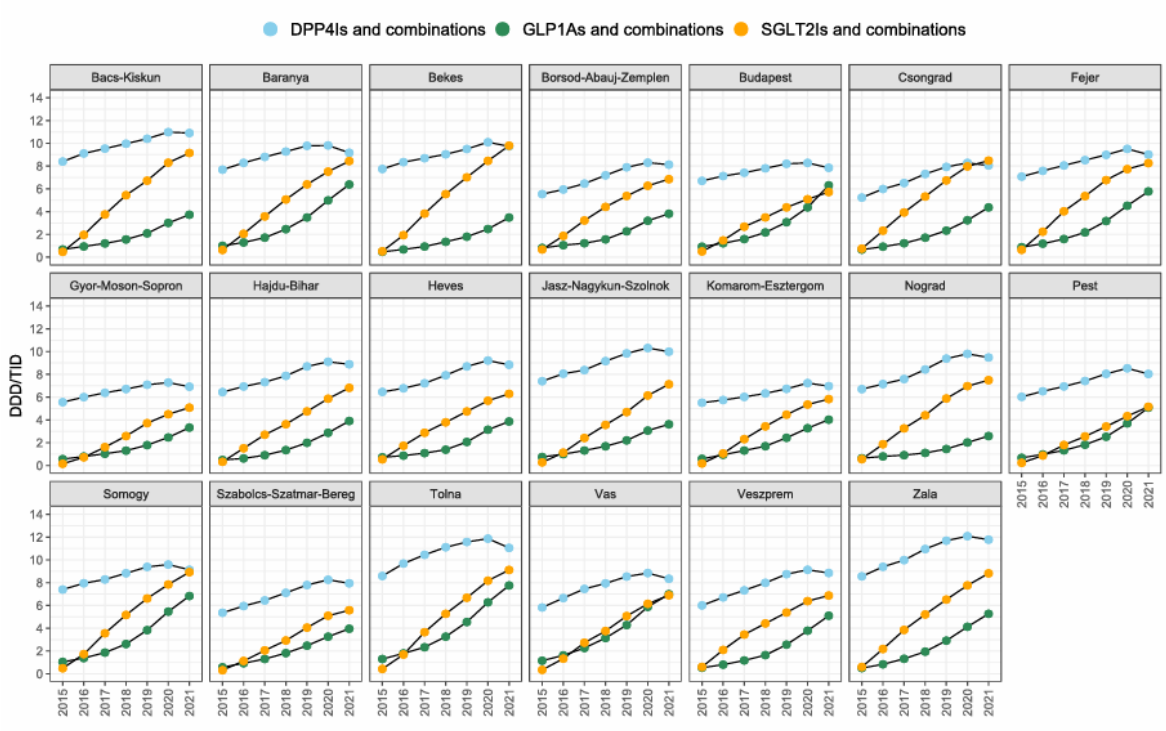
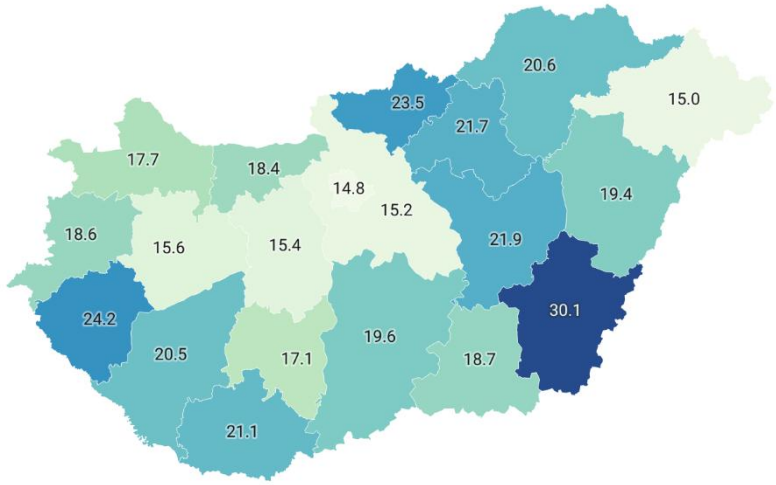
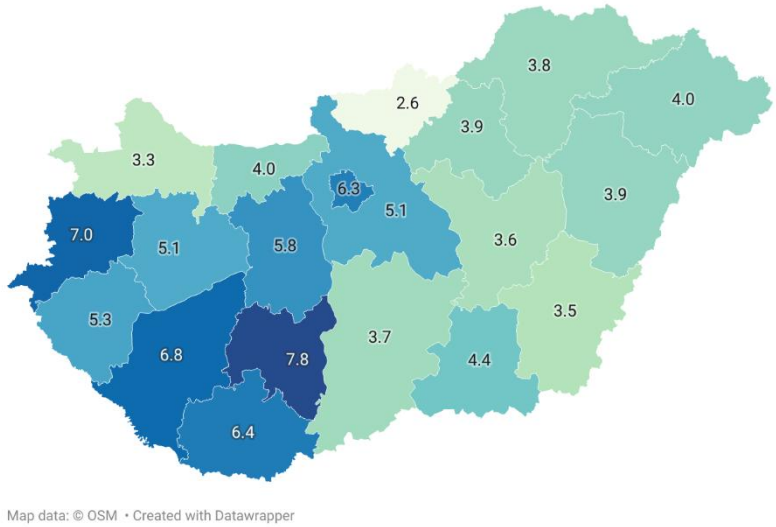

DPP4Is and combinations
GLP1As and combinations
SGLT2Is and combinations
DDD/TID
Bacs-Kiskun
Baranya
Bekes
Borsod-Abauj-Zemplen
Budapest
Csongrad
Fejer
Gyor-Moson-Sopron
Hajdu-Bihar
Heves
Jasz-Nagykun-Szolnok
Komarom-Esztergom
Nograd
Pest
Somogy
Szabolcs-Szatmar-Bereg
Tolna
Vas
Veszprem
Zala

Figure 3. Regional differences in the use of antidiabetic medication groups in 2021 (expressed in DDD/TID)

Regional differences in sulfonylurea use



Regional differences in the use of GLP1As and their combinations



Regional differences in the use of SGLT2Is and their combinations

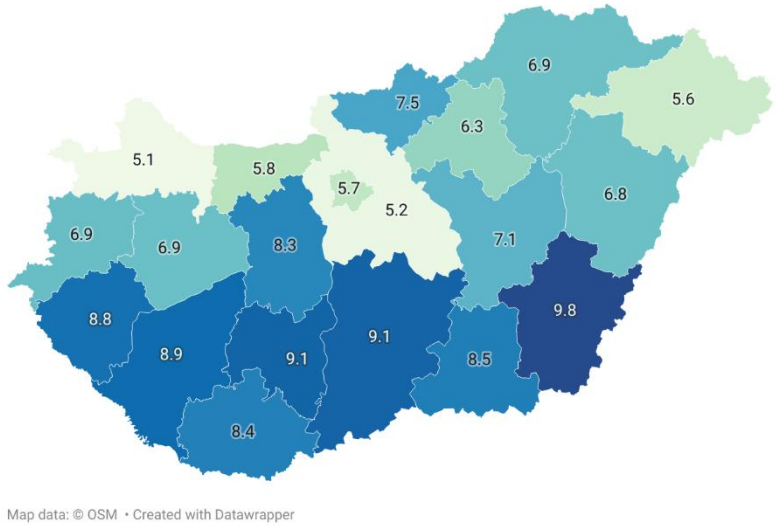
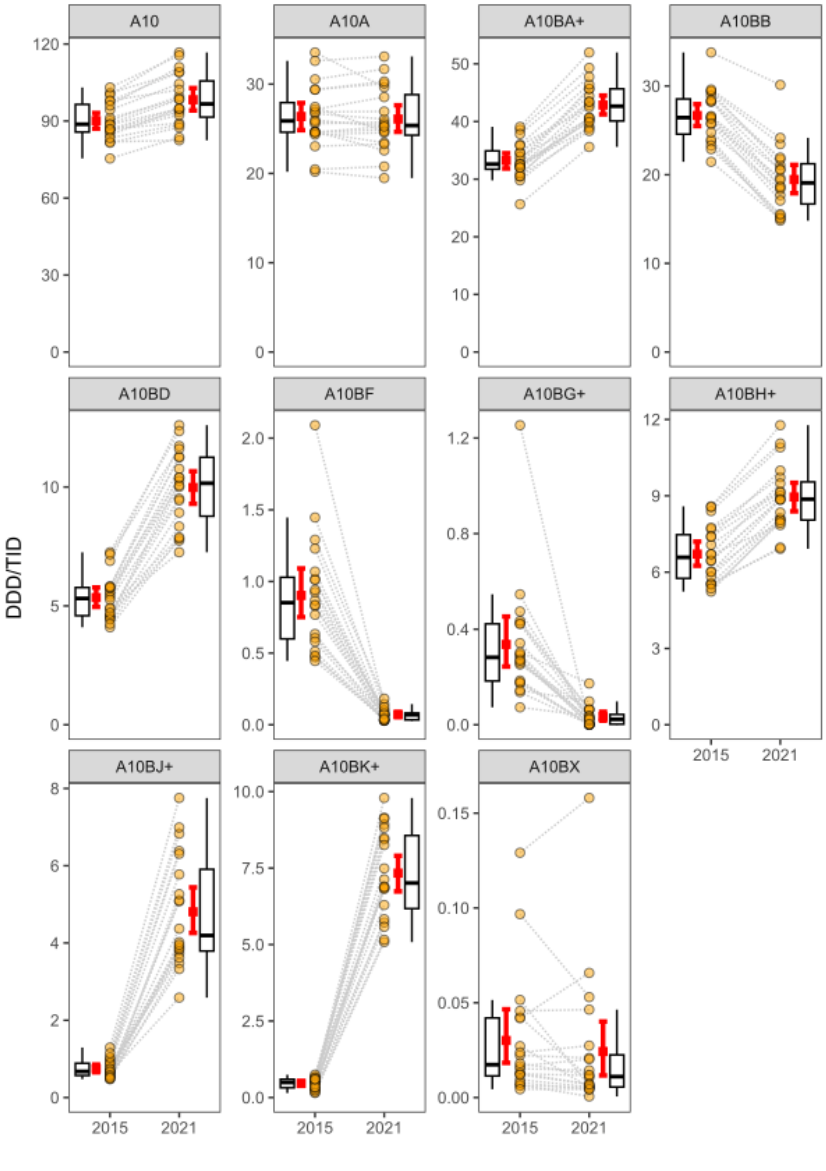


Figure 4. Change in regional antidiabetic drug group utilization between 2015 and 2021

Red square and lines: county average±95% CI; Yellow circle: county utilization data

A10: Antidiabetics total, A10A: Insulins, A10BA+: Biguanides and combinations, A10BB: Sulfonylureas, A10BD: Combinations of antidiabetics, A10BF: Alpha glucosidase inhibitors, A10BG+: Thiazolidindiones and combinations, A10BH+: dipeptidyl peptidase 4 inhibitors and combinations, A10BJ+: glucagon-like peptide-1 analogues and combinations, A10BK+: sodium-glucose co-transporter 2 inhibitors and combinations, A10BX: Glinides



The use of alpha glucosidase inhibitors, thiazolidinediones and glinides constantly decreased and were 0.07 DDD/TID, 0.04 DDD/TID and 0.03 DDD/TID in 2021, which was marginal compared to other antidiabetic subgroups. Therefore, these drug groups were not included in the tables and correlation analysis was not performed on these data.

4.2.2 Regional antidiabetic medication use and possible determinants

Regarding antidiabetic medication use and possible determinants, total antidiabetic medication use and almost all investigated drug subgroups correlated positively with the percentage of those 60 years and older among the total population and the number of attendances in diabetologic outpatient services per thousand inhabitants, except for GLP1As and human insulins. The unemployment rate correlated only with sulfonylurea use, and the number of public medical card holders per ten thousand inhabitants correlated only with human insulin and sulfonylurea use. The regional prevalence of diabetes did not correlate with the use of any of the investigated drug groups. GLP1As were the only antidiabetic drug group that did not correlate with any of the investigated factors. The associations between antidiabetic medication use and possible determinants are presented in Table 6.

Table 6. Associations between antidiabetic medication use and possible determinants

	Antidiabetics total	Insulins	Human insulins	Analogue insulins	Metformin and combinations	Sulfonylureas	DPP4Is and combinations	GLP1As and combinations	SGLT2Is and combinations
	Correlation coefficient (p value)								
Unemployment rate	0.021 (0.930)	0.262 (0.265)	0.116 (0.627)	0.180 (0.446)	-0.311 (0.182)	0.468* (0.038)	0.331 (0.154)	-0.386 (0.092)	0.198 (0.402)
Number of public medical card holders per ten thousand inhabitants	0.203 (0.391)	0.543* (0.013)	0.463* (0.04)	0.314 (0.177)	-0.104 (0.663)	0.466* (0.038)	0.313 (0.179)	-0.260 (0.268)	0.205 (0.387)
Regional prevalence of diabetes	0.171 (0.470)	0.126 (0.596)	0.132 (0.578)	-0.033 (0.890)	0.304 (0.193)	-0.119 (0.618)	0.059 (0.806)	0.251 (0.286)	0.209 (0.376)
Percentage of the 60 years and older among the total population	0.815* (<0.001)	0.602* (0.005)	0.173 (0.466)	0.576* (0.008)	0.553* (0.011)	0.651* (0.002)	0.741* (<0.001)	0.177 (0.454)	0.791* (<0.001)
Number of attendances in diabetologic outpatient service (diabetologists) per thousand inhabitants	0.694* (0.001)	0.670* (0.001)	0.294 (0.208)	0.568* (0.009)	0.536* (0.015)	0.479* (0.032)	0.501* (0.024)	0.174 (0.464)	0.656* (0.002)

Associations were tested with Spearman rank test. P values <0.05 showed statistical significance

5. DISCUSSION

5.1. Analysis using the National Health Insurance database

A retrospective analysis was conducted regarding changes in antidiabetic medication use in Hungary between 2008 and 2017. Our results showed that the antidiabetic medication utilization patterns changed remarkably during the study period. Since 2008, novel antidiabetic drugs and their fixed-dose combinations have constituted a major share of total antidiabetic medication use. Following authorization, novel antidiabetic drugs were soon included in therapeutic recommendations made both internationally and by the Hungarian Diabetes Association, which has contributed to their increased utilization [29-31]. The Hungarian diabetes therapeutic guideline included DPP4Is and GLP1As as early as 2009 when only exenatide, sitagliptin and vildagliptin were available. At that time, they were not listed as preferred agents, but only as options to be used in combination with metformin or sulfonylureas as a second or third drug [32]. SGLT2Is first appeared in the Hungarian therapeutic guideline in 2014, but only as an option combined with metformin [33]. In contrast, the next available Hungarian guideline in 2017 included DPP4Is as preferred agents in case of metformin intolerance or contraindication [7]. If people with diabetes did not achieve the recommended glycaemic target on metformin monotherapy, the Hungarian guideline included any of the novel antidiabetic drugs as recommended agents in combination with metformin [7]. While the American Diabetes Association (ADA) statement (2017) did not prioritize among novel antidiabetic drug groups when used after metformin or in combination with metformin, suggesting that drug choice should be based on individual factors, the 2019 version of the ADA statement does prioritize among novel antidiabetic drugs [5,34]. If people with diabetes have established atherosclerotic cardiovascular disease and/or chronic kidney disease, SGLTIs and GLP1As use have priority [5].

The increased use of novel antidiabetic drugs is not unique to Hungary. Complete national antidiabetic medication utilization data based on wholesaler’s database were also available for Estonia, Finland and Norway [35-43]. Novel antidiabetic drug consumption in these three countries showed a similar increasing tendency as Hungary, but there are some national differences. While novel antidiabetic drug utilization was similar in Hungary and Estonia, it was higher in Norway and even more so in Finland. Almost all novel antidiabetic drug groups showed an increasing rate of use in the investigated countries, but utilization was the greatest in Finland (Table 7). In Estonia and Norway, fixed-dose combinations of DPP4Is+SGLT2Is were already utilized during the study period, while in Hungary, these fixed-dose

combinations were not used before 2020 [35-40]. However, DPP4I or SGLT2I fixed-dose combinations with metformin or thiazolidinediones and GLP1A fixed-ratio combinations with insulins were available in Hungary (Table 7). Novel antidiabetic drugs received a 70% reimbursement in Hungary, while the reimbursement rate was 61% in Norway, 65% in Finland, and 50%, 75% or 90% in Estonia depending on different criteria (e.g., age, body mass index, previous treatment) [8, 44-47]. Both in Norway and in Finland there was an annual ceiling for co-payment, which means that after reaching the ceiling, people did not have to pay any co-payment for their medication for the remainder of the calendar year [44-46].

Table 7. Comparison of novel antidiabetic drug use of four countries shown in defined daily dose per thousand inhabitants per day (DDD/TID)

		2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
		DDD/TID									
Hungary	DPP4I	0.04	0.71	1.76	3.18	4.02	4.91	5.70	6.41	6.98	7.42
	GLP1A			0.06	0.20	0.24	0.35	0.63	0.86	1.13	1.48
	SGLT2I							0.02	0.41	1.45	2.76
	Total novel antidiabetic drug use (% of total antidiabetic drug use)	0.04 (0.1)	0.71 (1.1)	1.82 (2.6)	3.38 (4.5)	4.26 (5.6)	5.26 (6.7)	6.35 (8.2)	7.68(11)	9.56 (13)	11.66 (16)
	Total antidiabetic drug use	63.18	67.63	71.34	74.75	75.93	78.12	77.35	70.87	73.23	74.73
Estonia [20-22]	DPP4I	0.12	0.63	1.11	1.76	2.56	3.48	4.64	6.03	6.97	7.81
	GLP1A			<0.01	<0.01	0.18	0.45	0.83	1.16	1.42	1.53
	SGLT2I							0.02	0.47	1.30	2.16
	Total novel antidiabetic drug use (% of total antidiabetic drug use)	0.12 (0.3)	0.63 (1.5)	1.11 (2.5)	1.76 (3.7)	2.74 (5.2)	3.93 (7.2)	5.49 (9.6)	7.66 (13)	9.69 (16)	11.43 (18)
	Total antidiabetic drug use	40.15	41.16	45.23	47.15	52.57	54.74	57.47	59.66	61.35	62.47
Finland [23-25]	DPP4I	0.75	1.67	5.58	9.85	12.77	13.74	17.06	18.96	19.86	18.77
	GLP1A				0.45	1.19	1.45	1.94	2.37	3.02	2.85
	SGLT2I							0.36	0.84	2.91	5.04
	Total novel antidiabetic drug use (% of total antidiabetic drug use)	0.75 (1.0)	1.67 (2.1)	5.58 (6.7)	10.3 (12)	13.96 (16)	15.19 (18)	19.36 (22)	22.17 (25)	25.79 (28)	26.66 (29)
	Total antidiabetic drug use	77.54	79.89	83.27	84.22	84.97	85.96	88.24	90.06	92.62	91.85
Norway [17-19]	DPP4I	0.10	0.30	1.61	3.17	3.78	4.46	5.30	6.06	6.71	7.49
	GLP1A	0.04	0.08	0.14	0.49	0.92	1.22	1.47	1.78	2.05	2.47
	SGLT2I						0.08	0.74	1.39	2.10	3.06
	Total novel antidiabetic drug use (% of total antidiabetic drug use)	0.14 (0.3)	0.38 (0.8)	1.75 (3.7)	3.66 (7.7)	4.70 (10)	5.76 (12)	7.52 (16)	9.22 (19)	10.86 (21)	13.02 (24)
	Total antidiabetic drug use	45.52	46.28	47.58	47.31	46.82	46.90	48.21	49.77	51.44	53.58

DPP4I - Dipeptidyl peptidase 4 inhibitors; GLP1A- Glucagon-like peptide-1 receptor agonists; SGLT2I- Sodium-glucose co-transporter 2 inhibitors

In Hungary, the use of DPP4Is showed continuous growth between 2008 and 2017, and they were the most frequently used novel antidiabetic drug group every year during the study period. Sitagliptin, the most consumed DPP4I in Hungary, was the first available drug from this group and kept its leading position until 2017, while other DPP4Is such as alogliptin and saxagliptin appeared in the Hungarian drug market later (2010 and 2014), and played only a relatively small part in the overall DPP4I use. Linagliptin has a unique position among DPP4Is. Although it appeared in the consumption data only in 2012, its higher use may be explained by its pharmacokinetic properties. Linagliptin is excreted in faeces mainly unchanged and is therefore recommended for people with diabetes who have renal impairment [5,7]. The higher utilization of DPP4I fixed-dose combinations may be explained by their prices. The price of a fixed-dose combined DPP4I product was equal to or lower than the sum of the prices of monocomponent products in Hungary [8]. Additionally, using a combined product that contains two active ingredients in one tablet is more comfortable and practical for those who need dual therapy, which may result in increased persistence and adherence to the medication [48].

GLP1A is a specific novel antidiabetic drug group for Type 2 diabetes, which can be administered subcutaneously (oral GLP1A preparation has not been authorized until the end of the study period); these drugs are also available in combination with insulins. GLP1As, especially the fixed-ratio combinations with insulins, are the most expensive among novel antidiabetic drugs. Although drug group characteristics such as their antihyperglycemic potency, beneficial cardiovascular effects and weight-lowering effect are outstanding, and their use is steadily growing, this increase is lower than that of the other two novel antidiabetic drug groups [5,49]. However, further growth in GLP1A utilization is expected, because in 2019 international recommendations (American Diabetes Association Standards of Care in Diabetes, American Association of Clinical Endocrinologists and American College of Endocrinology Consensus Statements, American Diabetes Association and the European Association for the Study of Diabetes Consensus Report) advised using GLP1As in cases of established atherosclerotic cardiovascular disease or obesity [5,50,51].

SGLT2Is appeared on the drug market in 2014, and their use has been rapidly increasing in Hungary ever since. This rapid increase is similarly observed in Norway, Estonia and Finland (Table 7). During the study period, SGLT2Is were the newest drugs for the treatment of Type 2

diabetes mellitus with absolutely new and promising target of action. Even though dapagliflozin was the first available SGLT2I in Hungary, empagliflozin quickly and considerably became the most popular of the two, which may be attributed to its proven cardiovascular benefit [52]. The continuous increase in SGLT2I use is likely in the coming years, because of their proven benefit in cases of chronic kidney disease, heart failure and weight loss [5,50].

Although therapeutic recommendations and guidelines should be the primary determining factor in choosing the optimal pharmacotherapy for each individual, the prices and reimbursement rates of medicines can considerably influence the choice of therapy. In Hungary, novel antidiabetic preparations are reimbursed at 70%, so people have to pay a 30% co-payment. Human insulins are available with 100% reimbursement (people must pay only a small dispensing fee, 300 HUF) and other reimbursed oral antidiabetic drug groups are available with a 50-55% or 70% coverage [8]. As novel antidiabetic drugs are partially reimbursed, the increasing utilization of these preparations puts a financial burden not only on the health care system, but more so on people with diabetes. The higher expenses for individuals can be attributed to several factors. First, novel antidiabetic drugs are expensive agents among antidiabetic preparations. Second, although the insurer pays 70% of the novel antidiabetic drugs' price, these preparations result in relatively higher expenses for people than other cheaper drugs such as metformin, sulfonylureas or other expensive, but 100% reimbursed preparations such as human insulins. Although the insurer's novel antidiabetic drug expenditure share of the total antidiabetic medication reimbursement does not increase as steeply as individuals' share, this increase adds up to a considerable sum.

The decreasing utilization of sulfonylureas, alpha glucosidase inhibitors, thiazolidinediones, and meglinides coincides with the trends of other countries and follows Hungarian therapeutic guidelines [5,7,17,53]. Although both the ADA recommendation and the Hungarian therapeutic guidelines recommend metformin as a first-line agent in cases of Type 2 diabetes, in Hungary a sudden drop was seen in the use of metformin in 2015 [5,7]. This was due to the reimbursement withdrawal of one of the most commonly prescribed metformin preparations, and, consequently, its further use was not captured in the database. Since metformin is also available as a fixed-dose combination with several other oral antidiabetic drugs, the total use of metformin fixed-dose combinations is increasing.

It must be noted that our study has both strengths and limitations. The 10-year study period enabled us to observe the appearance of novel antidiabetic drugs on the drug market and to follow their increasing consumption. The NHIF database contains drug dispensing data for the entire Hungarian population; however, this database records data only on the sale of reimbursed medications. As a result, our data have total population coverage, but not total drug dispensing coverage because non-reimbursed drugs are not included in the database. Consequently, in our study, total metformin use could not be comprehensively recorded. This causes the under-measurement of metformin and total antidiabetic drug use, and subsequently results in an over-calculation of the relative share of novel antidiabetic drugs among the total use of antidiabetic drugs. At the same time, as novel antidiabetic drugs were reimbursed, a complete and detailed picture of the Hungarian novel antidiabetic drug tendencies was analyzed. It should also be noted that although the application of DDD/TID makes the comparison of aggregated medication use of different drug groups across populations possible, DDD may differ from the actual prescribed daily doses [24].

5.2. Analysis using wholesale database

This is the first study to analyze antidiabetic drug utilization in Hungary, including not only reimbursed but also non-reimbursed antidiabetics. It is also the first study to analyze antidiabetic medication use and its determinants at the regional level in Hungary. In recent years, substantial novelties in diabetes therapy and therapeutic protocols have impacted antidiabetic medication utilization patterns. This retrospective drug utilization study confirmed that antidiabetic medication use changed remarkably between 2015 and 2021 in Hungary.

In all Hungarian counties, total antidiabetic use emerged, but with an interesting peak in 2020. This utilization peak coincided with the Coronavirus Disease-19 outbreak when the Hungarian population tended to stock their chronic medications. This stockpiling effect was also observed in the medication utilization data of other nations [54].

Regarding antidiabetic subgroups, metformin was the most commonly used antidiabetic alone or in fixed-combination with other antidiabetic drugs (DPP4Is and SGLT2Is) during the entire study period. This was explained by the Hungarian guidelines where metformin is the first drug of choice alone or in combination if the patients are newly diagnosed with type 2 diabetes and do

not have HbA1c above 9% with catabolic symptoms [10]. The high rate of metformin use was similarly observed in Denmark, where metformin use was 39% of the total antidiabetic use in 2021 [55]. Sulfonylureas are still included in Hungarian and international therapeutic guidelines but not as preferred agents due to their side effects, such as hypoglycemia and weight gain, and furthermore, this drug group does not decrease the risk of major cardiovascular events [9,10,12]. Although sulfonylurea use has decreased continuously, its share of total antidiabetic medication use was still remarkable in Hungary. The utilization of sulfonylureas has shown high differences among some European countries. In Hungary the share of sulfonylurea use at the national level was 19.2% in 2021; in Denmark, it was only 3.6% in 2021, while in Romania, the sulfonylurea use was estimated to be 27.9% of the total antidiabetic medication use in 2019 [55,56]. Despite the growing prevalence of diabetes, insulin use remained relatively stable, while the utilization of newer antidiabetics, mainly SGLT2Is and GLP1As, has emerged dynamically. The use of newer antidiabetic groups 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 [57]. Additionally, while SGLT2Is and GLP1As have positive cardiovascular and renal effects, insulin has a neutral effect in this respect, but has a high risk of hypoglycemia and weight gain [9,10,12]. The emerging tendency of SGLT2I and GLP1A use and the change in the use of DPP4I in 2021 is partly due to the different place of these drug groups in therapeutic guidelines.

GLP1As and SGLT2Is are preferred agents in cases of established/high risk of atherosclerotic cardiovascular disease or chronic kidney disease [9,58]. In addition, SGLT2Is are preferred in cases of established/high risk of heart failure and GLP1As are preferred if the main goal is weight management above glycemic targets [9,58]. DPP4Is have neutral effects on weight and cardiovascular and renal problems with moderate effect on blood glucose control, and their use is preferred if the main goal is to improve glucose control without hypoglycemia in the case of elder, frail people [6,9]. The emerging use of DPP4Is, SGLT2Is and GLP1As use has also been observed in other countries' utilization data, such as Denmark or Portugal [14,55].

Regarding interregional differences, we found stable and considerable variability in the use of antidiabetics which had not been previously studied. Regional differences in total antidiabetic use remained stable and low, in contrast with some antidiabetic subgroups. Insulin use and its regional differences were relatively stable in all counties, and we did not find a geographical

gradient in the utilization pattern or association with regional diabetes prevalence. Although insulin use did not correlate with the unemployment rate, an association was found between insulin use and the number of public medical card holders per ten thousand inhabitants. The initiation of insulin therapy is not a financial issue, because human insulin preparations are available with 100% reimbursement (with only a minimal patient co-payment of 300 HUF/box), so the patient's financial situation has no influence on receiving insulin therapy [28]. However, if patients with type 2 diabetes need to receive insulin analogues that are more expensive, these preparations are available with 50% or 100% reimbursement coverage depending on the patients' HbA1c levels [8,28]. Therefore, patients with a poorer financial situation are more likely to receive human insulin therapy than the more expensive insulin analogues. This is supported by the positive association between human insulin use and the number of public medical card holders. The positive correlation between insulin use and the number of attendances in diabetologic outpatient service per thousand inhabitants may be explained by the fact that insulin can be prescribed with reimbursement only under regular diabetologist supervision [28]. The positive correlation between insulin use and the percentage of people with age 60 years or older can be explained by the fact that older people are more likely to have diabetes for a longer period of time, therefore, their diabetes is more likely to have progressed to the stage where insulin therapy is necessary to be initiated.

In the case of metformin, the relatively low difference in use among counties and the limited associations with socioeconomic factors may be explained by the high use of metformin in all counties because of therapeutic recommendations, and its affordability and availability. Metformin alone is relatively inexpensive and therefore does not impose a high financial burden on patients, and GPs can prescribe these agents without regular supervision by diabetologists [28]. Other fixed-dose preparations, mainly with DPP4Is and SGLT2Is, are available with 70% reimbursement, but only under regular diabetologist supervision [28].

In addition to the considerable utilization of sulphonylureas, we found high differences among counties. The high use of sulfonylureas in Hungary can be explained by some factors. Sulfonylureas are inexpensive agents, especially in contrast to newer drug groups, such as GLP1As, which are the most expensive antidiabetic drug group. In Hungary in 2021, the full price of sulfonylureas were approximately 25-52 HUF/DDD and available with 55%

reimbursement. Although GLP1As are available with 70% reimbursement coverage, their full price is much higher, at approximately 800-1240 HUF/DDD. Additionally, sulfonylureas, similar to metformin, are easily accessible because GPs can prescribe these drugs, while other drug groups (e.g., novel antidiabetic drug groups) can be prescribed with reimbursement only under regular diabetologists' supervision [28]. This seems to be confirmed by the positive associations with some socioeconomic factors such as unemployment rate, the number of public medical card holders per ten thousand inhabitants and the percentage of the 60 years and older among the total population.

Regarding DPP4I use, although the max/min difference between regions was 1.70 in 2021, a notable regional pattern and association with several socioeconomic factors could not be detected. Higher interregional differences were found in the case of SGLT2Is, and higher use was observed in southern counties; however, we did not find socioeconomic factors that clearly explain these differences. The utilization of GLP1As showed the largest interregional differences among antidiabetics (max/min ratio 3.00 in 2021). We did not find any socioeconomic factors that explained the detected southwest-northeast gradient. Although we did not detect an association with socioeconomic factors, many issues may have influenced the use of these drug groups. First, their price (mainly GLP1As and SGLT2Is) was significantly higher than that of metformin or SU. Second, these drugs can only be prescribed with reimbursement by GPs under the recommendations of diabetologists [28], which may complicate access to these medications for some patients. Additionally, most GLP1As are subcutaneous injections, which may be difficult for some patients to accept, although one orally administered GLP1A has been available since 2020.

Our data clearly show that drug choice depends not only on socioeconomic factors, but also on numerous other factors, which may be difficult to detect at the population level, as the choice of drug is highly individualized. We did not find any other studies that investigated the possible determinants of regional antidiabetic medication use. However, in one study that investigated geographical variation in antibiotic use and its possible determinants in Hungary, large interregional differences and associations with some socioeconomic factors were found [59].

Comparing the results of our study, which included both reimbursed and non-reimbursed medication use, to the results of our other study that was based only on reimbursed medication

use, it was revealed that there were considerable differences in the results. The overall use of antidiabetic medications was 24% higher in the wholesale dataset in 2015 compared to the use of only reimbursed medications. In the cases of most antidiabetic subgroups, the differences were very small (the lowest was for insulins being only 1.2%) but was enormous in the case of metformin. The overall use of metformin in our study was more than double than that of the reimbursed only metformin use. This can be explained by the fact that, while most antidiabetic medications are reimbursed, some widely used metformin products are not.

The present study had some strengths and limitations that must be considered. As far the strengths, first, to the best of our knowledge this is the first study to investigate both total national and interregional antidiabetic medication utilization trends and differences in Hungary. Second, the database covers total antidiabetic drug sales in Hungary, including both reimbursed and non-reimbursed medications, and our study has total population coverage (nearly 10 million people), which enables us to detect a complete and detailed picture of the national and interregional trends and differences in antidiabetic medication use.

Regarding the limitations of this retrospective study, a wholesale database containing antidiabetic medication sales for pharmacies was used. Due to the nature of the data source, it provides a slight overestimation of antidiabetic use, as not all medications acquired by pharmacies reach the patients for various reasons (e.g., medication expires before selling, damaged medications). In addition, the data were aggregated and it was not possible to distinguish between the drug claims of patients with type 1 and type 2 diabetes. Some antidiabetics, such as metformin, may be used for indications other than diabetes; however, our data did not contain information about indications of use. The database contains sales data of reimbursed and non-reimbursed medicines; however, differentiation among these drug categories was not possible in the present study. In some cases, data at the regional level were not available for potentially relevant determining factors.

6. CONCLUSIONS

A detailed picture of antidiabetic medication use patterns in Hungary was provided at both the national and regional levels including reimbursed and non-reimbursed medications. The last nearly 20 years have brought many changes in the treatment of diabetes mellitus. Since novel antidiabetic drugs appeared on the drug market, the utilization of these drugs has shown steady growth in Hungary. The reimbursement for novel antidiabetic drugs and their inclusion in the Hungarian therapeutic guidelines may be strong contributing factors to their increasing utilization. At the same time, the growing consumption of novel antidiabetic drugs put a high financial burden both on individuals and the national health care system. Although DPP4I, GLP1A and SGLT2I use was dynamically growing in Hungary, the share of sulfonylurea use was still considerable. Differences in antidiabetic drug consumption were substantial between regions, mainly in the case of GLP1As, SGLT2Is and sulfonylureas. The association between socioeconomic factors and regional drug use was confirmed mainly for sulfonylureas. The choice of therapy is highly individual and may depend on several patient- and healthcare-related factors; therefore, population level determining factors cannot necessarily explain regional differences. Future analysis of patient-level data may help identify patient-related and healthcare-related factors that possibly contribute to regional differences in antidiabetic medication use.

It should be noted that our studies aimed to analyze antidiabetic medication use at the population level and explore changes over time, but did not aim to evaluate the appropriateness of the choice of treatment, as it could only be performed on individual patient-level medication use and clinical data.

Recently, as a result of the intensive pharmacological research, a new active ingredient, the dual GIP and GLP1 receptor agonist tirzepatide, was authorized, and appeared in the drug market and many clinical researches are in progress (especially incretin-based peptides). These drugs may further reshape the prescription patterns of antidiabetics in the future [60,61].

Another notable issue is the extended new indication areas of antidiabetics. Incretins, such as GLP1A semaglutide and lixisenatide, and the dual GIP and GLP1 receptor agonist tirzepatide can be used not only in the case of diabetes mellitus but also in the treatment of obesity [62]. SGLT2Is such as empagliflozin and dapagliflozin, can be used in the treatment of chronic heart failure and chronic renal impairment [63].

Considering the facts mentioned above and the constant changes in both national and international guidelines and recommendations, a further increase in SGLT2I and GLP1A utilization and considerable emergence in expenses on antidiabetics is expected.

7. KEY MESSAGES

Analysis using the National Health Insurance Fund database:

• The use of reimbursed antidiabetic drugs (expressed in DDD/TID) increased continuously by 18% between 2008 and 2017 in Hungary.

• The use of novel antidiabetic drug groups (DPP4Is, GLP1As and SGLT2Is) has steadily increased, reaching 16% of the total antidiabetic drug consumption in 2017.

• Total expenditure on reimbursed antidiabetic medicines increased by 94% from 2008 to 2017. The use of novel antidiabetic drugs places a high financial burden both on people with diabetes and the healthcare system.

Analysis using wholesale database:

• We provided a detailed picture of antidiabetic medication use patterns in Hungary at both the national and regional levels between 2015 and 2021 including both reimbursed and non-reimbursed medication use.

• Although DPP4I, GLP1A and SGLT2I use was dynamically growing in Hungary, the share of sulfonylurea use was still considerable. In 2021, the share of novel antidiabetics was 19.2-24.1% between regions, and the share of sulfonylureas was 14.8–25.8% of total antidiabetic consumption.

• Differences in antidiabetic drug consumption were substantial between regions, mainly in the case of GLP1As (max/min ratio: 3.00), SGLT2Is (1.92) and sulfonylureas (2.03).

• The association between socioeconomic factors and regional drug use was confirmed mainly for sulfonylureas (in the case of unemployment rate and number of public medical card holders per ten thousand inhabitants).

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