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Research: Treatment

Use of glucose-lowering drugs in Hungary between 2008 and 2017: the increasing use of novel glucose-lowering drug groups

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Abstract

Aims To analyse glucose-lowering drug utilization, focusing on the novel glucose-lowering drug groups dipeptidyl peptidase-4 inhibitors, glucagon-like peptide-1 receptor agonists and sodium-glucose co-transporter-2 inhibitors, and the financial burden they entail.

Methods Crude reimbursed national drug utilization and expenditure data for the entire population of Hungary were obtained from the National Health Insurance Fund for the study period: 2008 to 2017. Data were analysed using the WHO's Anatomical Therapeutic Chemical Classification/defined daily dose system and were expressed in defined daily dose per 1000 inhabitants per day.

Results Total glucose-lowering drug consumption in Hungary showed an 18% increase over the study period, reaching 74.7 defined daily doses per 1000 inhabitants per day, while novel glucose-lowering drug use increased to 11.7 defined daily doses per 1000 inhabitants per day (16% of total glucose-lowering drug use) by 2017. Dipeptidyl-peptidase 4 inhibitor consumption grew to 7.4 defined daily doses per 1000 inhabitants per day by 2017. The most widely used dipeptidyl-peptidase 4 inhibitor was sitagliptin. Glucagon-like peptide-1 receptor agonists were used the least, but by 2017 rose to 1.5 defined daily doses per 1000 inhabitants per day, led by liraglutide. Sodium-glucose co-transporter-2 inhibitors appeared in the utilization data in 2014 and their consumption, mainly empagliflozin, reached 2.8 defined daily doses per 1000 inhabitants per day by 2017. The total expenditure on glucose-lowering drugs increased 94% between 2008 and 2017, and the total cost of novel glucose-lowering drug utilization comprised 44% of the total glucose-lowering drug expenditure in 2017.

Conclusions Both the use of and the financial burden posed by novel glucose-lowering drugs in Hungary increased steadily between 2008 and 2017. This increase is expected to continue.

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Introduction

Diabetes mellitus is a growing health problem. The global prevalence of diabetes has almost doubled in the last 30–40 years (4.7% in 1980 and 8.5% in 2014); in Hungary the prevalence of people diagnosed with diabetes reached 10% in 2015 [1,2]. As the global burden of diabetes has increased, diabetes management has received increasing attention. According to therapeutic recommendations, lifestyle changes (including nutrition therapy, physical activity, smoking cessation and education) are essential to type 2 diabetes management, alongside optimal pharmacotherapy [3]. While for type 1 diabetes insulin preparations play the main role in pharmacotherapy, pharmacological treatment options for type 2 diabetes are more diverse and have changed considerably. Although metformin remains the first-line agent, novel glucose-lowering drugs—dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 receptor agonists (GLP-1RAs) and sodium-glucose co-transporter-2 (SGLT2) inhibitors—have been developed, authorized and included in therapeutic guidelines and recommendations [3,4]. In Hungary, such drugs receive reimbursement from the National Health Insurance Fund [5].

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What's new?

- The use of glucose-lowering drugs has increased continuously over the past decade. Since 2008 the use of these medications in Hungary [expressed in defined daily dose per 1000 inhabitants per day (DDD/TID)] has grown by 18%.
- The use of novel glucose-lowering drug groups (dipeptidyl peptidase-4 inhibitors, glucagon-like peptide-1 receptor agonists and sodium-glucose co-transporter-2 inhibitors) has steadily increased, reaching 16% of the total glucose-lowering drug consumption (expressed in DDD/TID) in 2017.
- The total expenditure on glucose-lowering medicines has increased by 94% since 2008. Novel glucose-lowering drug use places a high financial burden both on people with diabetes and the healthcare system.

Drug utilization studies are essential to evaluate the trends and changes in medication use. They also provide the opportunity to explore how the availability of new drug groups may reshape prescribing patterns in certain health conditions. Although studies on glucose-lowering drug utilization changes have been conducted in Hungary and in several other countries, in recent years the use of novel glucose-lowering drug groups specifically has not yet been analysed in detail in Hungary [6–8].

In the present study, our aim was to analyse the changes in utilization of glucose-lowering medications, focusing on changes in consumption of novel glucose-lowering drug groups, and to explore the financial burden generated by these products in Hungary between 2008 and 2017.

Methods

Retrospective drug utilization analysis was conducted covering the period between 2008 and 2017. The data were obtained from the medication dispensing database of the Hungarian National Health Insurance Fund, the sole and mandatory health insurance provider in Hungary [5]. The National Health Insurance Fund database contains the following monthly aggregated utilization data on each reimbursed medication for the entire population of Hungary (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; and total reimbursement cost. In the case of reimbursed medication, the total retail cost is shared between the National Health Insurance Fund (reimbursement cost) and the individual with diabetes (co-payment).

The data were analysed using the WHO ATC/defined daily dose (DDD) system (version 2018) and were expressed in DDD per 1000 inhabitants per day (DDD/TID) [9]. DDD is the assumed average maintenance daily dose of the medication used for its main therapeutic indication in adults and DDD/TID is calculated with the following formula: [amount used in 1 year (mg) × 1000]/[DDD (mg) × population × 365] [9]. Using the technical unit DDD/TID enables researchers to express the use of drugs in a standardized way and makes it possible to compare medication use across populations of different sizes. DDD/TID may also give a rough estimation of the proportion of the population using a certain medication. For example, 10 DDD/TID can be interpreted as, on average, 1% of the population using the medication every day [10].

For the present study, we analysed drugs used for diabetes (ATC code: A10) with special emphasis on novel glucose-lowering drug groups. Regarding these novel glucose-lowering drug groups, medications with the following ATC codes were included: A10BH and A10BD07-13 for DPP-4 inhibitors; A10BJ, A10AE54 and A10AE56 for GLP-1RAs; A10BK, A10BD15 and A10BD20 for SGLT2 inhibitors.

Descriptive statistics were used to describe the sum of yearly medication use, and relative use was expressed as the proportion of total glucose-lowering drug use. Linear regression was applied to analyse trends in the consumption of glucose-lowering drug groups in cases where data for a minimum 5 years were available. Trends were described by the regression coefficient (average annual change) and significance (P value) of the regression coefficient. P values <0.05 were taken to indicate statistical significance.

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

Ethics

The data were aggregated and anonymous, therefore, ethical approval was not required.

Results

Utilization trends of glucose-lowering drugs

During the 10-year study period, the consumption of glucose-lowering drugs showed an 18% increase and reached 74.7 DDD/TID, although in 2015, there was a drop in total glucose-lowering medication use (Table 1). Total insulin use rose by 41%, to 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 have begun to play an increasing role and reached 6.9 DDD/TID by 2017. α-glucosidase inhibitors, thiazolidinediones

Table 1 Use of reimbursed glucose-lowering drugs in Hungary between 2008 and 2017

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 to 0.94)*
A10AE54, 56	Insulin+GLP-1RAs									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 to 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 to –0.59)*
A10BD	Combinations of oral blood glucose-lowering drugs	1.91	2.19	2.8	3.09	3.44	4.01	4.61	5.11	5.91	6.92	0.53 (0.46 to 0.6)*
A10BD03, 05	Metformin+thiazolidinediones	1.87	1.74	1.5	0.72	0.44	0.36	0.29	0.24	0.21	0.17	–0.2 (–0.28 to –0.13)*
A10BD04	Sulfonylureas+thiazolidinediones	0.04	0.05	0.04	<0.01							
A10BD07, 08, 10, 11, 13	Metformin+DPP-4 inhibitors	0.01	0.40	1.26	2.37	3.00	3.65	4.32	4.85	5.22	5.5	0.65 (0.57 to 0.73)*
A10BD09	Thiazolidinediones+DPP-4 inhibitors								<0.01	0.01	0.01	
A10BD15, 20	Metformin+SGLT2 inhibitors								0.02	0.48	1.23	
A10BF	α-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 to –0.1)*
A10BG	Thiazolidinediones	0.15	0.22	0.22	0.18	0.12	0.11	0.1	0.09	0.07	0.07	–0.02 (-0.02 to –0.01)*
A10BH	DPP-4 inhibitors	0.04	0.31	0.5	0.81	1.02	1.26	1.38	1.56	1.74	1.91	0.21 (0.19 to 0.22)*
A10BJ	GLP-1RAs			0.06	0.2	0.24	0.35	0.63	0.86	0.86	0.94	0.14 (0.11 to 0.17)*
A10BK	SGLT2 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 to –0.01)*
	Total novel glucose-lowering 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 to 1.38)**
	Total glucose-lowering 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 to 1.91)*

DDD/TID, defined daily dose per 1000 inhabitants per day; DPP-4, dipeptidyl peptidase 4; GLP-1RA, glucagon-like peptide-1 receptor agonists; SGLT2, sodium-glucose co-transporter-2.
Novel glucose-lowering drugs include GLP-1RAs, DPP-4 inhibitors and SGLT2 inhibitors.
*$P<0.05$; regression coefficient describes trends showing the average annual changes.

and meglinides were less commonly used and their consumption steadily decreased over the study period (Table 1).

Utilization trends of novel glucose-lowering drugs

From 2008, total novel glucose-lowering drug use increased constantly and significantly, from 0.04 DDD/TID to 11.7 DDD/TID, which was the largest increase among all glucose-lowering drug groups during the study period (Table 1). The proportion of novel glucose-lowering drugs rose to 16% of total glucose-lowering medication use by 2017 (Table 2).

During the past 10 years, the most widely used novel glucose-lowering drug group comprised the DPP-4 inhibitors, which first appeared on the Hungarian market in 2008. Their consumption showed dynamic growth and reached 7.4 DDD/TID in 2017 (Table 2). Aggregated DPP-4 inhibitor use was 64% of the total novel glucose-lowering drug consumption in 2017. While sitagliptin monocomponent products constituted the majority of DPP-4 inhibitor use in 2008, in 2017 three-quarters of the total DPP-4 inhibitor 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, in recent years, utilization decreased (Table 2).

Among the novel glucose-lowering drugs, GLP-1RAs accounted for the lowest utilization rates, although they did show an increase in use over time. GLP-1RAs appeared in the National Health Insurance Fund database in 2010 and, by 2017, their use was 1.5 DDD/TID, 13% of total novel glucose-lowering drug consumption. Fixed-ratio combinations (mainly insulin degludec + liraglutide and less often insulin glargine + lixisenatide) represented one-third of the total GLP-1RA consumption, while monocomponent medications represented two-thirds of GLP-1RA utilization in 2017. The most commonly used monocomponent product in 2017 was liraglutide, followed by dulaglutide, lixisenatide and exenatide (Table 2).

Although SGLT2 inhibitors 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 total novel glucose-lowering drug use in 2017. The utilization of monocomponent SGLT2 inhibitor preparations increased dynamically and reached 1.5 DDD/TID, while the use of SGLT2 inhibitors + metformin was slightly lower in 2017. Approximately two-thirds of the total SGLT2 inhibitor utilization comprised empagliflozin and its combinations (Table 2).

Financial burden of novel glucose-lowering drugs

The increased utilization of novel glucose-lowering drugs has resulted in higher healthcare expenditure for both individuals with diabetes and the National Health Insurance Fund because these drugs have a considerably higher price than other glucose-lowering drugs. Comparing the average retail prices (reimbursement + co-payment) per DDD, among subcutaneous preparations, GLP-1RAs are 4.4–5.7 times more expensive than human insulins. Among oral glucose-lowering drugs, DPP-4 inhibitors cost 12.3–15.4 times more than metformin, and SGLT2 inhibitors are 14.6 times more expensive than metformin. Total expenditure on glucose-lowering medications has increased by 94% since 2008, reaching 50.04 bn HUF (EUR 161.4 m) in 2017. Within total glucose-lowering medication expenditure, the share of novel glucose-lowering drugs has grown substantially. By 2017, the total cost of novel glucose-lowering drug utilization accounted for 44% of the total glucose-lowering medication expenditure (Fig. 1). As all novel glucose-lowering drugs were reimbursed medications, both the health insurance provider's and individuals' expenditure on these drugs have risen significantly since 2008, but to a different extent. In 2017, novel glucose-lowering drugs comprised a 39% share of the National Health Insurance Fund's total reimbursement expenditure on glucose-lowering drugs, while 63% of co-payment for glucose-lowering drugs was spent on novel glucose-lowering drugs (Fig. 1).

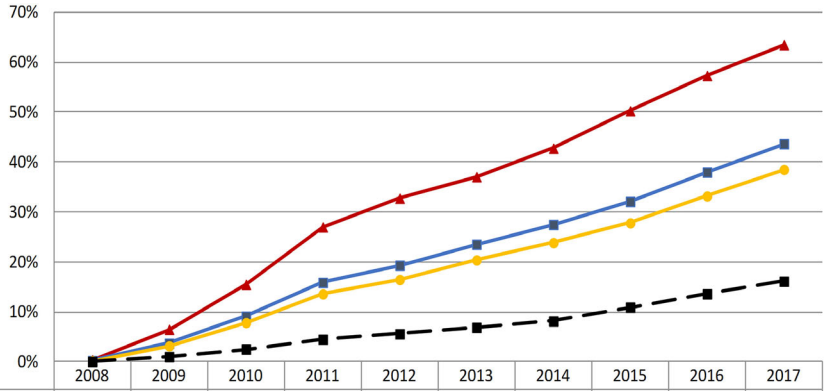
Discussion

The present retrospective analysis of the changes in glucose-lowering medication use in Hungary between 2008 and 2017 shows that glucose-lowering medication utilization patterns have changed remarkably during the last 10 years. Since 2008, novel glucose-lowering drugs and their fixed-dose combinations have constituted a major proportion of total glucose-lowering medication use. Soon after being approved for use, novel glucose-lowering drugs were included in therapeutic recommendations made both internationally and by the Hungarian Diabetes Association, which has contributed to their increasing utilization [11–13]. The Hungarian diabetes therapeutic guidelines included DPP-4 inhibitors and GLP-1RAs as early as 2009, when only exenatide was 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 a third drug [14]. SGLT2 inhibitors first appeared in the Hungarian therapeutic guidelines in 2014, but only as an option combined with metformin [15]. In contrast, the latest guidelines include DPP-4 inhibitors as preferred agents in case of metformin intolerance or contraindication [4]. If people with diabetes do not achieve the recommended glycaemic targets while receiving metformin monotherapy, the Hungarian guidelines include any of the novel glucose-lowering drugs as recommended agents in combination with metformin [4]. Although the American Diabetes Association statement in 2017 did not prioritize any novel glucose-lowering drug group over another when used after metformin or in combination with metformin, suggesting instead that drug choice should be based on individual factors, the

Table 2 Use of novel glucose-lowering drugs between 2008 and 2017 in Hungary

ATC code		2008 DDD/TID	2009	2010	2011	2012	2013	2014	2015	2016	2017
	DPP-4 inhibitors 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
	GLP-1RAs 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
	SGLT2 inhibitors 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 glucose-lowering drug use (% of total glucose-lowering 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 glucose-lowering drug use	*63.18*	*67.63*	*71.34*	*74.75*	*75.93*	*78.12*	*77.35*	*70.87*	*73.23*	*74.73*

DDD/TID, defined daily dose per 1000 inhabitants per day; DPP-4, dipeptidyl peptidase 4; GLP-1RA, glucagon-like peptide-1 receptor agonists; SGLT2, sodium-glucose co-transporter-2.



	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
Novel glucose-lowering drugs share from total glucose lowering drug co-payment*	0.4%	6.5%	16%	27%	33%	37%	43%	50%	57%	63%
Novel glucose-lowering drugs share from total glucose-lowering drug cost**	0.2%	3.7%	9.1%	16%	19%	24%	27%	32%	38%	44%
Novel glucose-lowering drugs share from total glucose-lowering drug reimbursement***	0.2%	3.2%	7.9%	14%	16%	20%	24%	28%	33%	39%
•Novel glucose- lowering drugs share from total glucose lowering 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 glucose-lowering drug groups: comparison of the increase in utilization of and increase in expenditure (total cost, reimbursement and co-payment) on the novel glucose-lowering drugs as a proportion of the total reimbursed glucose-lowering drugs. Total cost is shared between the National Health Insurance Fund (reimbursement) and individuals (co-payment). *Increase in individuals' expenses, expressed as the share of novel glucose-lowering drug co-payment (30% of total price) as a proportion of the total glucose-lowering drug co-payment. **Increase of total drug expenditure (co-payment+reimbursement), expressed as the share of novel glucose-lowering drug expenditure as a proportion of the total glucose-lowering drug expenditure. ***Increase in the expenditure of the National Health Insurance Fund, expressed as the share of novel glucose-lowering drug reimbursement (70% of total price) as a proportion of the total glucose-lowering drug reimbursement. ****Increase in novel glucose-lowering drug use [defined daily dose per 1000 inhabitants per day (DDD/TID)] as a proportion of the total glucose-lowering drug use (DDD/TID).

2019 version does recommend that, in people with diabetes who have established atherosclerotic cardiovascular disease and/or chronic kidney disease, the use of SGLT2 inhibitors and GLP-1RAs should have priority [3,16].

The increasing use of novel glucose-lowering drugs is not unique to Hungary. Complete national glucose-lowering medication utilization data based on wholesalers' databases were also available for Estonia, Finland and Norway [17–25]. Novel glucose-lowering drug consumption in these three countries showed a similarly increasing trend to that in Hungary, but there are some national differences. While novel glucose-lowering drug use was similar in Hungary and Estonia, it was higher in Norway and even higher in Finland. Almost all novel glucose-lowering drug groups had increasing rates of use in the investigated countries, but utilization was greatest in Finland (Table 3). In Estonia and Norway, fixed-dose combinations of DPP-4 inhibitors + SGLT2 inhibitors were already utilized during the study period, while in Hungary these fixed-dose combinations were not used [17–22]; however, DPP-4 inhibitor or SGLT2 inhibitor fixed-dose combinations with metformin or thiazolidinediones and GLP-1RA fixed-ratio combinations with insulins were available in Hungary (Table 2). Novel glucose-lowering drugs are eligible for 70% reimbursement in Hungary, while the reimbursement rate is 61% in Norway, 65% in Finland, and in Estonia it can be 50%, 75% or 90% depending on different criteria (e.g. age, BMI, previous treatment) [5,26–29]. Both in Norway and in Finland there is an annual ceiling for co-payment; after reaching the ceiling, individuals do not have to pay any co-payment for their medication for the remainder of the calendar year [26,28].

In Hungary, the use of DPP-4 inhibitors has shown continuous growth over the past 10 years, and this was the most frequently used novel glucose-lowering drug group in every year of the study period. Sitagliptin, the most commonly used DPP-4 inhibitor in Hungary, was the first available drug from this group and kept its leading position during the last 10 years, while other DPP-4 inhibitors, such as alogliptin and saxagliptin, appeared on the Hungarian drug market later (2010 and 2014), and constituted only a relatively small part of overall DPP-4 inhibitor use. Linagliptin has a unique position among DPP-4 inhibitors. 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 [3,4]. The higher rate of utilization of DPP-4 inhibitor fixed-dose combinations may be explained by their prices. The price of a fixed-dose combined DPP-4 inhibitor product was equal to or lower than the sum of the prices of the monocomponent products in Hungary [5]. Additionally, using a combined product that contains two active ingredients in one tablet is more comfortable and practical for those who need dual therapy,

Table 3 Comparison of novel glucose-lowering drug use in four countries

		2008 DDD/TID	2009	2010	2011	2012	2013	2014	2015	2016	2017
Hungary	DPP-4 inhibitor	0.04	0.71	1.76	3.18	4.02	4.91	5.70	6.41	6.98	7.42
	GLP-1RA			0.06	0.20	0.24	0.35	0.63	0.86	1.13	1.48
	SGLT2 inhibitor							0.02	0.41	1.45	2.76
	Total novel glucose-lowering drug use (% of total glucose-lowering 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 glucose-lowering 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]	DPP-4 inhibitor	0.12	0.63	1.11	1.76	2.56	3.48	4.64	6.03	6.97	7.81
	GLP-1RA			<0.01	<0.01	0.18	0.45	0.83	1.16	1.42	1.53
	SGLT2 inhibitor							0.02	0.47	1.30	2.16
	Total novel glucose-lowering drug use (% of total glucose-lowering 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 glucose-lowering 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]	DPP-4 inhibitor	0.75	1.67	5.58	9.85	12.77	13.74	17.06	18.96	19.86	18.77
	GLP-1RA				0.45	1.19	1.45	1.94	2.37	3.02	2.85
	SGLT2 inhibitor							0.36	0.84	2.91	5.04
	Total novel glucose-lowering drug use (% of total glucose-lowering 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 glucose-lowering 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]	DPP-4 inhibitor	0.10	0.30	1.61	3.17	3.78	4.46	5.30	6.06	6.71	7.49
	GLP-1RA	0.04	0.08	0.14	0.49	0.92	1.22	1.47	1.78	2.05	2.47
	SGLT2 inhibitor						0.08	0.74	1.39	2.10	3.06
	Total novel glucose-lowering drug use (% of total glucose-lowering 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 glucose-lowering drug use	45.52	46.28	47.58	47.31	46.82	46.90	48.21	49.77	51.44	53.58

DDD/TID, defined daily dose per 1000 inhabitants per day; DPP-4, dipeptidyl peptidase 4; GLP-1RA, glucagon-like peptide-1 receptor agonists; SGLT2, sodium-glucose co-transporter-2.

which may result in increased persistence and adherence to the medication [30].

The GLP-1RAs represent a specific novel glucose-lowering drug group for type 2 diabetes that can be administered subcutaneously; these drugs are also available in combination with insulins. GLP-1RAs, in particular, the fixed-ratio combinations with insulins, are also the most expensive among novel glucose-lowering drugs. Although drug group characteristics such as their anti-hyperglycaemic potency, beneficial cardiovascular effect and weight-lowering effect are outstanding, and their use is steadily growing, this increase in use is smaller than that observed for the other two novel glucose-lowering drug groups [3,31]. Further growth in GLP-1RA utilization is expected, however, because recent consensus statements and recommendations advise using GLP-1RAs, mainly liraglutide, instead of or in combination with metformin, in case of established atherosclerotic cardiovascular disease or obesity [3,32].

The SGLT2 inhibitor class of drugs appeared on the drug market in 2014 and their use has been rapidly increasing in Hungary ever since. This rapid increase is similarly observable in Norway, Estonia and Finland (Table 3). SGLT2 inhibitors are the newest drugs in the treatment of type 2 diabetes mellitus, with a completely new and promising target of action. Although dapagliflozin was the first available SGLT2 inhibitor in Hungary, empagliflozin quickly became the considerably more popular of the two, which may be attributed to its proven cardiovascular benefit [33]. The continuous rise of SGLT2 inhibitor use is likely in the coming years, because of their proven benefit in case of chronic kidney disease, heart failure and weight loss [3,32].

Although therapeutic recommendations and guidelines should be the primary determining factor in choosing the optimal pharmacotherapy for each individual, the price and reimbursement rate for a medicine can considerably influence therapy. In Hungary, all novel glucose-lowering preparations are reimbursed at 70%, so the co-payment rate for individuals is 30%, while human insulins are available with 100% reimbursement (individuals are required to pay only a small dispensing fee) and reimbursed oral glucose-lowering drug groups are available with 50–55% or 70% reimbursement rates [5]. As novel glucose-lowering drugs are partially reimbursed, the increasing use of these preparations puts a financial burden not only on the healthcare system, but also, and more so, on people with diabetes. The higher cost for individuals can be attributed to several factors. Firstly, novel glucose-lowering drugs are expensive compared with other glucose-lowering preparations. Secondly, although the insurer pays 70% of the novel glucose-lowering drug price, these preparations involve greater expense for the individual than do cheaper drugs, such as metformin and sulfonylureas, or other expensive but 100% reimbursed preparations, such as human insulins. Although the insurer's share of novel glucose-lowering drug expenditure in relation to the total glucose-lowering medication reimbursement is not increasing as steeply as the individuals' share, this increase adds up to a considerable sum.

The decrease in use of sulfonylureas, α-glucosidase inhibitors, thiazolidinediones and meglinides follows the pattern observed in other countries and is in step with Hungarian therapeutic guidelines [3,4,7,34]. Although both the American Diabetes Association and the Hungarian therapeutic guidelines recommend metformin as a first-line agent in case of type 2 diabetes, in Hungary, a sudden decrease was seen in the use of metformin in 2015 [3,4]. 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 glucose-lowering drugs, the total use of metformin fixed-dose combinations is increasing.

The present study has both strengths and limitations. The 10-year study period enabled us to observe the appearance of novel glucose-lowering drugs on the market and to follow their increasing consumption. The National Health Insurance Fund 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 since non-reimbursed drugs are not included in the database. Consequently, total metformin use could not be comprehensively recorded. This leads to the under-measurement of metformin and total glucose-lowering drug use, and subsequently an over-calculation of the relative share of novel glucose-lowering drugs among the total use of glucose-lowering drugs. At the same time, because all novel glucose-lowering drugs were reimbursed, a complete and detailed picture of the trends in use of novel glucose-lowering drugs in Hungary was available for analysis. 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, the DDD may differ from the actual prescribed daily dose [10].

In conclusion, the last 10 years have brought many changes in the treatment of diabetes mellitus. Since novel glucose-lowering drugs appeared on the drug market, the use of these drugs has grown steadily in Hungary. The reimbursement for novel glucose-lowering 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 glucose-lowering drugs puts a high financial burden both on individuals and the national healthcare system. Considering the constant changes in both national and international guidelines and recommendations, a further increase in novel glucose-lowering drug utilization is expected.

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Competing interests

None declared.

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