The Analysis of the Development of Metformin and Sulfonylurea Prescriptions in the Czech Republic

Denisa Janíčková-Žďárská[1], Petr Honěk[2], Ladislav Dušek[3,4], Tomáš Pavlík[3,4], Milan Kvapil[1]

[1] Department of Internal Medicine, 2nd Faculty of Medicine, Charles University, Prague, and Motol University Hospital, Praha, Head Prof. MUDr. Milan Kvapil, CSc., MBA
[2] The General Health Insurance Company of the Czech Republic, Praha, Head Ing. Zdeněk Kabátek
[3] The Institute of Health Information and Statistics of the Czech Republic, Praha, Head doc. RNDr. Ladislav Dušek, Ph.D.
[4] The Institute of Biostatistics and Analyses MU, Brno, Head doc. RNDr. Ladislav Dušek, Ph.D.

Summary
Introduction: In the Czech Republic, patients with diabetes mellitus (DM) are followed and treated predominantly by specialists (approx. 80% at a specialist diabetology clinic), a minor part by general practitioners (up to 20%). Long-term development of the changes in prescribing metformin and sulfonylurea in the Czech Republic and its concordance with recommended procedures has not been evaluated until now. **Goal:** Comparison of the development of metformin (MET) and sulfonylurea (SU) prescriptions in the period of 2002–2006 with that of 2010–2014 in a representative sample of the patient population with DM kept in the database of the General Health Insurance Company of the Czech Republic (VZP) which provided health care coverage for 63% of Czech Republic population in 2014. **Methodology:** We identified all individuals in the VZP database who had a record of DM diagnosis (E10 – E16 based on ICD 10) or who had any antidiabetic therapy prescribed (ATC group A10) in the periods of 2002–2006 and 2010–2014. A cohort of patients was extracted for analysis, who had an agent from A10 group prescribed at least once in a rele-vant year (n = 308 962 in 2002; n = 426 695 in 2014). A number of patients was evaluated for each year, who had at least once MET or SU prescribed. The number of patients treated with MET or SU was then expressed as a percentage of all who had any therapy from A10 group prescribed in the year in question. **Results:** Metformin prescriptions have linearly risen from 43% to 77%, while sulfonylurea prescriptions have linearly decreased from 65% to 37%. **Conclusion:** The analysis presents the first evaluation of the development of metformin prescriptions conducted in the Czech Republic and evaluation of its concordance with the recommended procedures for the treatment of DM. The amount of metformin prescribed in the Czech Republic increased from 43% to 77% while the amount of SU prescribed decreased from 65% to 37% between 2002 and 2014. This development and the current ratio between the prescribed amounts of MET and SU demonstrate the implementation of the recommended procedures into practice and prove the high quality of care for patients with DM2T in specialists – diabetologists' surgeries.

Key words: type 2 diabetes mellitus – metformin – sulfonylurea

Introduction

The only relevant public source in the Czech Republic which displays information about the therapy of diabetes mellitus (DM) is the statistics of the Institute of Health Information (ÚZIS) [1]. It does not allow for evaluation of the changes in the structure of therapy and their development over time.

Since the publication of the UKPDS study results [2] metformin has been preferred as a pharmacological intervention of first choice for patients with type 2 diabetes (DM2T); it holds this position over the long term in the recommended procedures for the treatment of DM2T of the Czech Diabetes Society within the Czech Medical Association of J.E. Purkyně [3]. There has been no study published so far, however, that would evaluate the long-term development of the changes in prescribing metformin and sulfonylurea in the Czech Republic. Therefore it has not been possible to evaluate the extent to which the specialist recommendations are adhered to.

In the Czech Republic patients with diabetes mellitus are followed and treated predominantly by specialists (approx. 80% at a specialist diabetes clinic), a minor part by general practitioners (up to 20%). [4].

The aim of the study

The aim of our retrospective epidemiological analysis was to compare the development of the prescriptions

for metformin and sulfonylurea in the period of 2002–2006 with its development from 2010–2014 in a representative sample of the Czech population of patients with DM registered in the General Health Insurance Company of the Czech Republic (VZP) which provided health care coverage for 63% of Czech population in 2014.

Methodology

We identified all individuals in the VZP database, who in the periods of 2002 – 2006 and 2010–2014 had a record of DM diagnosis (E10 – E16 based on MKN 10) [5], or who had any antidiabetic therapy prescribed (ATC group A10) [6]. Subsequently a set of patients was extracted for analysis, who had any agent from the group A10 prescribed at least once in the given year. For each year we evaluated a number of individuals who had metformin prescribed at least once (regardless of any other antidiabetic therapy, separately or in a fixed-dose combination), or sulfonylurea (regardless of any other antidiabetic therapy, separately or in a fixed-dose combination). The number of patients treated with metformin or sulfonylurea was then expressed as a percentage of all who had any therapy from the group A10 prescribed in the year in question. All the data concerning patients is identified in the original database for one person by a personal identification number. The data provided by VZP and used for analysis was blinded by conversion on an anonymous identifier which however enables tracing of all prescriptions and medical practices relating to a particular person.

Results

Table 1 shows the number of individuals diagnosed with DM who were identified in the VZP database in the individual years, and the number of individuals who had any therapy from the group A10 prescribed at least once in the given year. Chart 1 represents the development of the proportional shares of prescriptions for metformin and for sulfonylurea in the individual years. A marked linear increase in the prescriptions of

Table 1 . The number of individuals with DM identified in VZP database in individual years based on the present diagnosis of diabetes mellitus (n) and **the number of individuals for which any therapy from group A10 (N) was prescribed at least once in a given year**

year	2002	2003	2004	2005	2006	2010	2011	2012	2013	2014
n	618 011	606 090	599 006	591 025	582 120	794 819	781 084	754 899	729 034	769 558
N	308 962	312 061	318 024	326 613	333 933	388 050	407 205	414 673	418 582	426 695
MET (%)	43.2	45.4	47.5	50.3	52.6	70.3	72.5	74.3	75.6	77.0
SU (%)	65.2	63.5	61.6	59.0	58.0	46.1	43.5	41.3	39.4	37.2

MET – The number of individuals who had metformin prescribed in the given year in any combination, expressed as percents of all individuals who had antidiabetic medication prescribed **SU**– the number of individuals who had sulfonylurea prescribed in the given year in any combination, expressed as percents of all individuals who had antidiabetic medication prescribed

Chart 1 . Prevalence of prescriptions of metformin (MET) and sulfonylurea (SU) in the Czech Republic in the periods of 2002–2006 and 2010–2014 expressed in percents of all individuals who had any antidiabetic medication prescribed in a given year
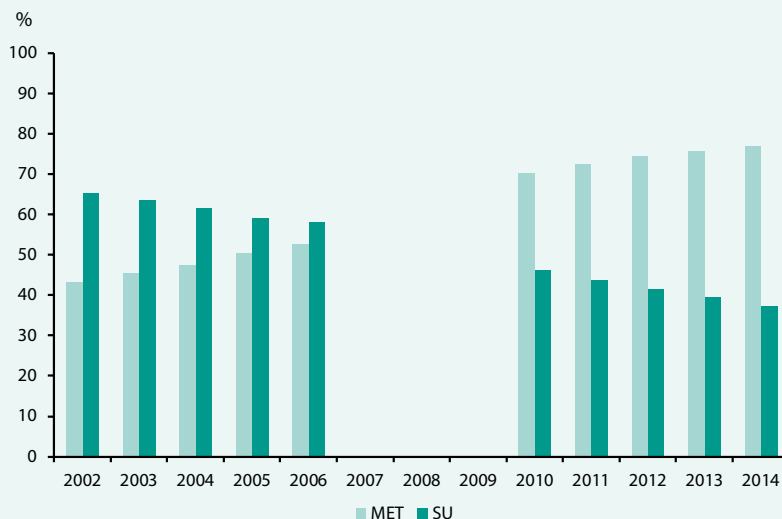
metformin is seen, from 43 % to 77 % of all patients who had antidiabetic medication prescribed, as well as a decrease in sulfonylurea prescriptions from 65 % to 37 %. Of all the patients treated with insulin only in 2013, 14 % were 0–39 years old and 7 % were 40–49 years old. These patients are in all likelihood treated for type 1 diabetes mellitus.

Discussion

According to the present recommendations, the initial therapy for DM2T involves lifestyle adjustments (diet and exercise), weight reduction and metformin therapy (MET) [3]. The pharmacological intervention for an asymptomatic patient should always be indicated with regard to life expectancy which may be significantly limited by comorbidities (oncological disease, advanced heart failure) [7]. The position of MET as a first choice medicine for therapy of DM2T was postulated based on the results of the UKPDS study [8,9]. This recommendation is only being put into practice in gradual steps. On the general level the delay can be accounted for by certain conservatism characteristic of the medical profession, by the lack of evidence proving that it would benefit patients, provided they are satisfactorily compensated, if they were transferred from sulfonylurea (SU) to MET, so this therapy had been introduced at first as only initial therapy. Another reason in the Czech Republic was certainly the difference in price. Finally, the fact that the opinion on MET as being beneficial also for patients treated with insulin had developed gradually over time, also played a role. The presented data confirm the steady increase in the prescriptions for MET over time. The gradual decrease in SU prescriptions is in particular caused by two facts – it increases the risk of hypoglycemia and accelerates the natural loss of insulin secretion [2,10,11], as a result of which the patient requests ultimate extension of therapy. An exception within the SU group is gliclazide in the galenic form with slow release. It involves a lower risk of hypoglycemia compared to glimepiride [12]. Its exceptional quality in relation to safety has been confirmed by the ADVANCE study [13].

The basic cohort of individuals in the VZP database who have a diagnosis of DM assigned at some times, is much larger than it is probably consistent with an actual number of individuals followed and treated for DM. If we applied the number of individuals from 2013 to the whole population by means of extrapolation based on the number of insurees, we would get 1 157 196 patients treated for diabetes in the Czech Republic. This number does not correspond to the ÚZIS data (861 647 in 2013) [4]. The ÚZIS data is confirmed by two independent investigations in the general population older than 18 years, undertaken in the last quarter of 2014, in which 8 % of the respondents said they were treated for diabetes [14]. The overestimation of the number can be explained by the diagnosis of DM being entered e.g. on requests for laboratory tests in the case of suspicion of diabetes, which is subsequently disproved, and suchlike. As the majority of people diagnosed with DM are treated by specialists, it can be expected that those whose prognosis is defined inter alia by a consistent effort to normalize glycemia, have also antidiabetic therapy prescribed in accordance with the recommended procedures. Performing the same extrapolation then shows that this reasoning is correct. Based on the extrapolation from VZP data 664 415 individuals in the Czech Republic have any type of therapy for DM prescribed. According to the ÚZIS data there were 721 689 individuals pharmacologically treated in 2013. Therefore we consider the conditions specified by us for the selection of the cohort with the aim of assessing the trends in prescriptions of MET and SU in the Czech Republic relevant and providing data which reflect the situation in the whole Czech Republic. Numerous published epidemiological studies also consider only pharmacologically treated patients [15,16,18].

We used the whole cohort of individuals for analysis who had antidiabetic medication prescribed. Our cohort also includes individuals with DM1T and other types of diabetes. This composition was chosen because of a significant ambiguity involved in determining the type of diagnosis according to MKN 10 specified in the VZP database (from 2010 to 2014 the diagnoses E10 and E11 were specified for 17.7 % of patients). We consider the distortion caused by the inclusion of patients with DM1T irrelevant to the final evaluation, since the number of patients with DM1T only changes slightly (7.1 % in 2002 and 6.8 % in 2013) [4], and therefore cannot essentially impact the overall trend. It may be concluded, in favour of the thesis that the recommended procedures are implemented with great efficiency in the Czech Republic, that provided the number of patients younger than 40 treated with insulin in 2013 was deducted, the number of patients treated with MET would increase by 1 %.

Our analysis testifies to the real practice in the Czech Republic, that means, it also considers patients with serious comorbidities and limited life expectancy, as well as patients exposed to minimum risk. The resulting proportion of those treated with MET in 2014 is comparable with the share of MET within the therapy of the population at high cardiovascular risk in large-scale clinical studies which assess cardiovascular safety of the new antidiabetic drugs, as shown in Tab. 2. This comparison supports the fact that the care given to the population of patients with DM2T is at a high level of quality in the Czech Republic. Table 2 shows the decrease in the absolute number of patients kept in the VZP database with a diagnosis of DM. This decrease is caused by the gradual loss of individuals insured with VZP. According to the ÚZIS data the trend in the whole of the Czech Republic is opposite – a sustained increase in the prevalence of DM [4].

The analysis of prescriptions is based on the VZP data. That means that the collected and paid for prescriptions

Table 2 Percents of patients treated with metformin when joining the study. Modified acc. to [20–24]

	TECOS	EXAMINE	SAVOR TIMI	ORIGIN	EMPA –REG	ČR 2014
active therapy	81.0	65.0	69.9	27.0	73.8	77.0
placebo	82.2	67.4	69.2	27.8	74.3	

are considered. In this way the bias of non-compliance is removed concerning a patient who has medication prescribed but fails to collect it. Still it cannot be ruled out that part of the collected medicines is not used by the patient.

The limitation of the analyses drawing on the VZP database at present consists in the impossibility of estimating, with high likelihood, the kind of initial therapy for diabetes. This will be possible after further years of monitoring have been added; this will enable identification of individuals for whom the diagnosis of diabetes is also supported, apart from a diagnosis record, by the first prescription for antidiabetic therapy. A study conducted in Quebec on a limited population of individuals with DM receiving primary care identified an increase in prescribing metformin as the first-line antidiabetic drug from 89.7 to 94.6 % between the years 2002 and 2011 [15]. These values imply a suspicion, however, that a selected population was involved. The presence of comorbidities does not allow for treating 95% of individuals with MET in a non-selected population of patients with DM2T.

The presented data comes close to the published results from other countries. Comparison is very difficult, primarily because of the different methods used. We see the benefit of our analysis in its covering a large part of the whole Czech population with diabetes mellitus, unlike local studies in which selected physicians are engaged and the studies therefore do not offer a coherent view of the level of care as a whole in the given country [15–18].

A study evaluating trends in the prescription of antidiabetic drugs among the population over 60 years of age by means of analysis of 6 databases in the province of Ontario (Canada), showed an increase in the number of patients treated with MET from 56.2 % in 2002 to 76.5 % in 2013 [16]. Within the same time-period the number of patients treated with glibenclamide decreased from 56.4 % to 10.7 %: following the introduction of gliclazide to the market in 2007 there were 24.3 % individuals treated with it in 2013. The prescription of glimepiride was not evaluated in the study, as it amounted to < 5 %. The prescription of insulin remained practically unchanged, during the course of the period under evaluation the number of hospitalizations for hypoglycemia significantly decreased.

The Swedish National Diabetes Register was analyzed on the basis of the MET therapy results in a recent publication from which the summary prevalence of the prescription of MET can also be derived within a 5-year period [17]. The primary aim of the analysis was to evaluate the cardiovascular risks in different therapies, involving a pharmacologically treated population with DM2T aged 40–85 years. All patients in the register who met the entrance criteria and who were recorded in the period of 2004–2007 were included. Of the overall number of 51 675 persons, 59 % were treated with MET and 80 % with SU.

A study by Ingrid Leal et al [18] was primarily focused on the analysis of the prescription of rosiglitazone, however the prevalence of the prescription of MET in the evaluation cohort of 178 674 individuals with DM2T increased from 8.7 to 22.7 % between the years 2000–2009.

Conclusion

The analysis presents the first evaluation of the development of metformin prescriptions in the Czech Republic and of its concordance with the recommended procedures for the treatment of DM. A marked linear increase in the prescriptions of metformin is observed, from 43 % to 77 % of all patients who had antidiabetic medication prescribed. Within the same period a significant decrease in the prescriptions of SU from 65 % to 37 % took place as a counter movement. This development and the current ratio between the prescribed amounts of MET and SU confirm the implementation of the recommended procedures into practice and prove the high quality of care for patients with DM2T at the specialist diabetes clinics, also evidenced by other positive results such as the trend of a decreasing incidence of amputations [19].

Literature

1. Ústav zdravotnicvkých informací. Dostupné z WWW: <http://www.uzis.cz>.

2. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. Lancet 1998; 352(9131): 837–853.

3. Česká diabetologická společnost. Doporučený postup péče o diabetes mellitus 2. typu. Dostupné z WWW: <http://www.diab.cz/dokumenty/dm2_12.pdf>. (poslední přístup 26. 9. 2015)

4. Ústav zdravotnických informací a statistiky ČR. Diabetologie, péče o diabetiky. Dostupné z WWW: <http://www.uzis.cz/category/tematicke-rady/zdravotnicka-statistika/diabetologie-pece-diabetiky>. (26. 9. 2015)

5. Ústav zdravotnických informaci. Mezinárodní statistická klasifikace nemocí a přidružených zdravotních problémů – MKN-10. Dostupné z WWW: <http://www.uzis.cz/cz/mkn/index.html>. (poslední přístup 26. 9. 2015)

6. WHO Collaborating Centre for Drug Statistics Methodology. Anatomical Therapeutic Chemical (ATC) classification system. Structure and principles. Dostupné z WWW: <http://www.whocc.no/atc/structure_and_principles/>. (poslední přístup 26. 9. 2015)

7. Inzucchi SE, Bergenstal RM, Buse JB et al. Management of hyperglycaemia in type 2 diabetes, 2015: a patient-centred approach. Update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetologia. 2015; 58(3): 429–442.

8. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group. Lancet 1998; 352(9131): 854–865. Erratum in: Lancet 1998; 352(9139):1558.

9. Holman RR, Paul SK, Bethel MA et al. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med 2008; 359(15): 1577–1589.

10. Matthews DR, Cull CA, Stratton IM et al. UK Prospective Diabetes Study (UKPDS) Group. UKPDS 26: Sulphonylurea failure in non-insulin-dependent diabetic patients over six years. Diabet Med 1998; 15(4): 297–303.

11. Kahn SE, Haffner SM, Heise MA et al. ADOPT Study Group. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. N Engl J Med 2006; 355(23): 2427–2443.

12. Schernthaner G, Grimaldi A, Di Mario U et al. GUIDE study: double-blind comparison of once-daily gliclazide MR and glimepiride in type 2 diabetic patients. Eur J Clin Invest 2004; 34(8): 535–542.

13. ADVANCE Collaborative Group. Patel A, MacMahon S, Chalmers J et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med 2008; 358(24): 2560–2572.

14. Kvapil, M. Měly by nás zajímat názory občanů na léčbu diabetu? Kazuistiky v diabetologii 2015; 13(1): 4–5.

15. Wang TY, Eguale T, Tamblyn R. Guidelines adherence in the treatment of patients with newly diagnosed type 2 diabetes: a historical cohort comparing the use of metformin in Quebec pre and post-Canadian Diabetes Association guidelines. BMC Health Serv Res 2013; 13: 442. Dostupné z DOI: <http://dx.doi.org/10.1186/1472–6963–13–442>.

16. Clemens KK, Shariff S, Liu K et al. Trends in Antihyperglycemic Medication Prescriptions and Hypoglycemia in Older Adults: 2002–2013. PLoS One 2015; 10(9): e0137596. Dostupné z DOI: <http://dx.doi.org/10.1371/journal.pone.0137596>.

17. Ekström N, Schiöler L, Svensson AM et al. Effectiveness and safety of metformin in 51 675 patients with type 2 diabetes and different levels of renal function: a cohort study from the Swedish National Diabetes Register. BMJ Open 2012; 2(4): pii: e001076. Dostupné z DOI: <http://dx.doi.org/10.1136/bmjopen-2012–001076>.

18. Leal I, Romio SA, Schuemie M et al. Prescribing pattern of glucose lowering drugs in the United Kingdom in the last decade: a focus on the effects of safety warnings about rosiglitazone. Br J Clin Pharmacol 2013; 75(3): 861–868.

19. Piťhová P, Honěk P, Dušek L et al. Incidence amputací u pacientů s diabetes mellitus v České republice 2010–2014. Vnitř Lék 2015; 61(11 Suppl 3): 3S21–3S24.

20. Green JB, Bethel MA, Armstrong PW et al. TECOS Study Group. Effect of Sitagliptin on Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med 2015; 373(3): 232–242.

21. White WB, Cannon CP, Heller SR et al. EXAMINE Investigators. Alogliptin after acute coronary syndrome in patients with type 2 diabetes. N Engl J Med 2013; 369(14): 1327–1335.

22. Scirica BM, Bhatt DL, Braunwald E et al. SAVOR-TIMI 53 Steering Committee and Investigators. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. N Engl J Med 2013; 369(14): 1317–1326.

23. ORIGIN Trial Investigators. Gerstein HC, Bosch J, Dagenais GR et al. Basal insulin and cardiovascular and other outcomes in dysglycemia. N Engl J Med 2012; 367(4): 319–328.

24. Zinman B, Wanner C, Lachin JM et al. EMPA-REG OUTCOME Investigators. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. N Engl J Med 2015. [Epub ahead of print].

as. MUDr. Denisa Janíčková-Žďárská, Ph.D.
✉ **denisa.janickova.zdarska@email.cz**

Department of Internal Medicine 2nd LF UK and FN Motol, Praha
www.fnmotol.cz