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Insulin Fact Sheet in Type 1 and 2 Diabetes Mellitus and Trends of Antidiabetic Medication Use in Insulin Users with Type 2 Diabetes Mellitus: 2002 to 2019

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Background: This study investigated the trends of insulin use among Korean patients with type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM). Changes in prescription of antidiabetic medications in T2DM patients taking insulin therapy were evaluated.
Methods: We analyzed data from the National Health Insurance Service database in Korea to evaluate the prevalence of insulin users and trends of insulin use in T1DM and T2DM patients from January 2002 to December 2019. We also investigated numbers and types of antidiabetic medications in insulin users with T2DM.
Results: The overall total number of insulin users increased from 2002 to 2019, reaching 348,254 for T2DM and 20,287 for T1DM in 2019 compared with 109,974 for T2DM and 34,972 for T1DM in 2002. The proportion of patients using basal analogs and short acting analogs have increased and those using human insulin, premixed insulin, or biphasic human insulin have decreased (rapid acting analogs: 71.85% and 24.12% in T1DM and T2DM, respectively, in 2019; basal analogs: 76.75% and 75.09% in T1DM and T2DM, respectively, in 2019). The use of other antidiabetic medication in addition to insulin increased for T2DM, especially in dual therapy, reaching up to 52.35% in 2019 compared with 16.72% in 2002.
Conclusion: The proportion of the patients using basal or rapid acting analogs increased among all insulin users in both T1DM and T2DM patients. Among patients with T2DM, the proportion of patients using antidiabetic medications in addition to insulin was significantly increased compared to those who used insulin alone.

Keywords: Diabetes mellitus, type 1; Diabetes mellitus, type 2; Hypoglycemic agents; Insulin

INTRODUCTION

The prevalence of diabetes mellitus (DM) worldwide is steadily increasing, and thus the treatment of DM has become an important social and economic issue. The Korean Diabetes Association (KDA) has been publishing the Diabetes Fact Sheet

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since 2012; according to the report published in May 2022, approximately six million Korean adults aged 19 years or older are estimated to have DM. Among patients with DM aged 30 years or older, 7.5% patients are estimated to use insulin [1]. Insulin treatment is necessary for all people with type 1 diabetes mellitus (T1DM) and a subgroup of people with type 2 diabetes mellitus (T2DM) who are no longer able to reach an appropriate glycemic target with oral antidiabetic medication alone or those who have hyperglycemic symptoms or catabolic features [2]. Patients with T1DM typically require initiation with multiple daily injections (basal [long acting] insulin and bolus [short acting] insulin) or continuous subcutaneous insulin infusion. The preferred regimen of insulin initiation in T2DM patients is starting basal insulin in addition to oral antidiabetic agents. If glycemic target is not achieved, bolus insulin can also be added to control postprandial glucose levels in T2DM patients.

After the first successful extraction of insulin from dog pancreas in 1921, the subsequent development of human recombinant insulin such as humulin R (rapid acting) and N (intermediate acting) was achieved [3]. The Diabetes Control and Complications Trial (DCCT) in 1993 found that the intensive treatment of diabetes delays the onset and slows the progression of microvascular complications in T1DM [4]. The development of short and long acting insulin analogs and their combination therapy has enabled more physiologic and intensive glycemic control without hypoglycemia, which is a major limiting factor of intensive glycemic control. Treatment with the analog insulins is associated with not only less hypoglycemia and weight gain but also lower glycosylated hemoglobin (HbA1c) compared with human insulin in T1DM patients [5]. The American Diabetes Association recently recommended a glucagon-like peptide-1 receptor agonist (GLP-1 RA), which is preferred to insulin when possible in T2DM, and there are diverse anti-diabetes treatment options [6]. Treatment intensification for patients who do not meet treatment goals should not be delayed and insulin is one of the important antidiabetic treatment options. Therefore, insulin treatment continues to play a necessary and important role for effective patient treatment. From this point of view, it is meaningful to investigate the current status of insulin use and the use of antidiabetic agents among insulin users.

In this study, we investigated the trends of insulin therapy in people with T1DM and T2DM in Korea. The trends of antidiabetic drug use among patients with T2DM who use insulin were also evaluated.

METHODS

Data source

We used a database from the National Health Insurance Service (NHIS) in Korea from January 2002 to December 2019. The Korean National Health Insurance (NHI) is a single health care insurance system that covers all residents in Korea. Information about medical utilization, patients' demographic data, prescription data, and diagnostic codes based on International Classification of Disease 10th revision (ICD-10) are assembled into the NHIS claim dataset. We examined the all the prescriptions of insulin claimed with T1DM and T2DM at all ages and the use of antidiabetic medication in insulin users with T2DM. This study was approved by the Institutional Review Board (IRB) of Samsung Medical Center (IRB number: SMC 2020-04-130). An informed consent exemption was granted by the IRB because all data provided by the NHIS to researchers were de-identified.

Study population

Patients who were prescribed insulin at least once in an outpatient clinic (not in-hospital prescription) claimed with ICD-10 code E10 or E11-14 from January 2002 to December 2019 were included. Patients prescribed insulin claimed with ICD-10 code E10 were defined as insulin users with T1DM and those prescribed insulin with ICD-10 code E11-14 were defined as insulin users with T2DM. If multiple insulin prescriptions were claimed in a year, the last claimed ICD-10 code for that year was used. ICD-10 code was included regardless of primary or secondary diagnosis. The patients prescribed insulin claimed with both E10 and E11-14 or without ICD-10 code of diabetes were excluded. The presence and type of diabetes were ascertained every year.

Classification of insulin and antidiabetic agents

We identified all types of insulin prescribed from January 2002 to December 2019 and classified the types into four categories: (1) human insulin, (2) premix insulin or biphasic human insulin (BHI), (3) rapid acting analogs, or (4) basal analogs [7]. The combinations of insulin types were so diverse that users of each type of insulin were counted in duplicate, whether or not they used another type of insulin. To investigate patients with more intensive insulin therapy, patients using a rapid acting analog alone, long acting analog alone, and long acting analog and rapid analog together were evaluated. Antidiabetic agents

were classified into eight categories: (1) metformin, (2) sulfonylureas, (3) dipeptidyl peptidase-4 (DPP-4) inhibitors, (4) sodium glucose cotransporter 2 (SGLT2) inhibitor, (5) thiazolidinedione, (6) meglitinides, (7) α-glucosidase inhibitor, and (8) GLP-1 RA.

RESULTS

Baseline characteristics of total insulin users

This study examined patients over a total 18 years, from 2002 to 2019. Table 1 shows the characteristics of insulin users in 2002, 2009, and 2019. The number of patients who received insulin more than once in outpatient clinic increased over time, with 368,541 in 2019. The mean age showed a tendency to increase, and the proportion of patients over 70 years increased.

Table 1. Baseline characteristics of total insulin users

	2002	2009	2019
Insulin user	144,946	279,405	368,541
Age, yr	57.8±13.4	59.6±13.9	62.0±14.8
<10	384 (0.26)	439 (0.16)	579 (0.16)
10–19	1,701 (1.17)	3,023 (1.08)	4,071 (1.10)
20–29	3,873 (2.67)	6,284 (2.25)	8,827 (2.40)
30–39	9,243 (6.38)	16,234 (5.81)	20,208 (5.48)
40–49	22,159 (15.29)	40,179 (14.38)	38,467 (10.44)
50–59	38,113 (26.29)	68,086 (24.37)	79,577 (21.59)
60–69	47,637 (32.87)	81,902 (29.31)	101,894 (27.65)
70–79	19,296 (13.31)	53,616 (19.19)	85,664 (23.24)
≥80	2,540 (1.75)	9,642 (3.45)	29,254 (7.94)
Male sex	71,050 (49.02)	145,020 (51.90)	206,508 (56.03)
Income			
Medical aid	2,518 (1.74)	35,774 (12.80)	41,375 (11.23)
Quartile 1	22,597 (15.59)	41,898 (15.00)	67,857 (18.41)
Quartile 2	29,295 (20.21)	46,159 (16.52)	60,158 (16.32)
Quartile 3	36,975 (25.51)	62,109 (22.23)	7,995 (21.69)
Quartile 4	53,561 (36.95)	93,465 (33.45)	119,200 (32.34)
Place, urban	70,797 (48.84)	127,054 (45.47)	159,628 (43.31)
Antidiabetic drug	62,503 (43.12)	159,752 (57.18)	267,034 (72.46)
Diabetes type			
Type 1	34,972 (24.13)	46,011 (16.47)	20,287 (5.50)
Type 2	109,974 (75.87)	233,394 (83.53)	348,254 (94.50)
Both types[a]	5,117	8,959	12,102

Values are presented as mean±standard deviation or number (%).
[a]These patients were excluded from this study.

Male and antidiabetic drug users also increased significantly. Regarding the ICD-10 code claimed when prescribing insulin, the prevalence of E10 (T1DM) decreased from 24.13% in 2022 to 5.50% in 2019 and E11-14 (T2DM) increased from 75.87% in 2002 to 94.50% in 2019.

Trends of insulin prescription in type 1 and 2 diabetes mellitus

The changing pattern of insulin prescription from 2002 to 2019 in T2DM is presented in Fig. 1 and Supplementary Table 1. The total number of insulin users with T2DM has increased since 2002. The use of human insulin has decreased since 2007 and the use of basal analogs has steadily increased since 2004 in T2DM. Fig. 1 depicts these trends. Supplementary Table 2 presents the trends of insulin prescription in T1DM. The number of total insulin users increased until 2011, but it has been decreasing since then. The use of human insulin has decreased since 2006, and the use of premix or BHI has also decreased since 2013. The proportion of rapid acting analogs and basal analogs users among total insulin users with T1DM has increased steadily (rapid acting analogs: 5.73% in 2002, 17.11% in 2009, 71.85% in 2019; basal analogs: 6.23% in 2005, 49.27% in 2011, 76.75% in 2019). When we further investigated insulin users who only use rapid acting analogs or basal analogs and patients who use basal analog plus rapid acting analogs in T1DM and T2DM, the proportion of insulin users using basal analogs plus rapid acting analogs has increased steadily and the users using basal analogs only has decreased since 2016 in T1DM (Supplementary Table 3). In T2DM, basal analog users and basal analog plus rapid acting analog users have increased steadily since 2005, up to 17.4% and 51.8%, respectively (Fig. 2, Supplementary Table 4).

Trends of antidiabetic medication use in type 2 diabetes mellitus

Among patients who use insulin with T2DM, the proportion of patients who only use insulin and not with other antidiabetic medication has been decreasing since 2002 (Supplementary Table 5). The patients who take one antidiabetic medication in addition to insulin increased until 2011 and then decreased from 2012 to 2019. The proportion of patients who take two antidiabetic medications other than insulin has steadily increased, reaching 52.4% until 2019; after 2015, it increased rapidly (Supplementary Table 5). Fig. 3 shows the overall trend of combinations of antidiabetic medication. Table 2 shows data

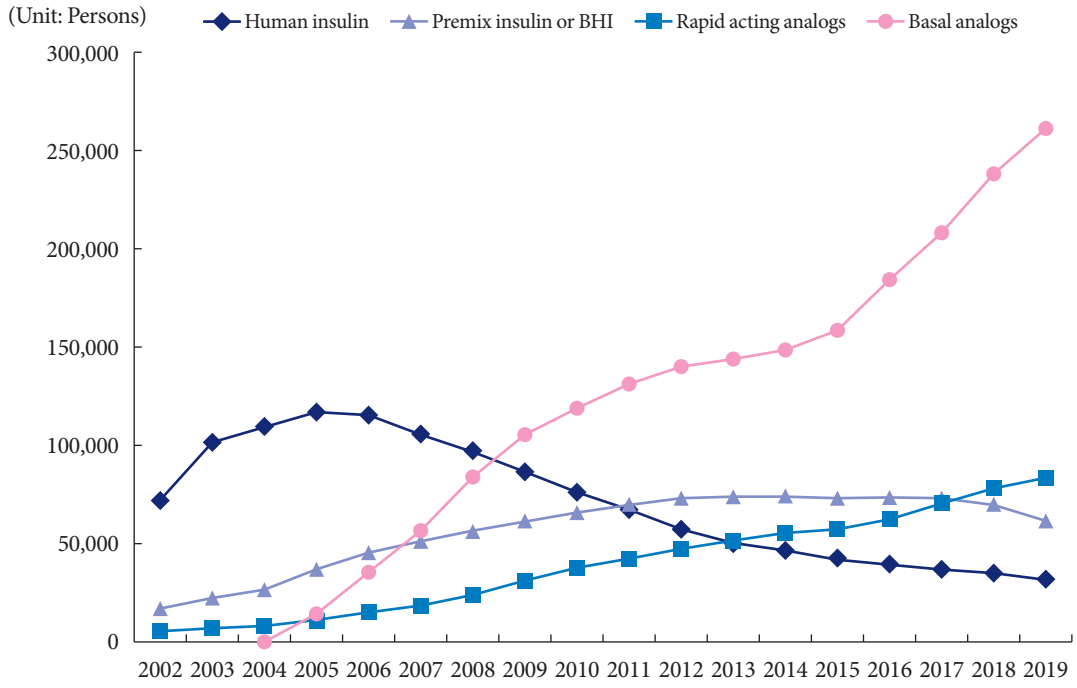

Fig. 1. Trends in insulin prescription in type 2 diabetes mellitus. BHI, biphasic human insulin.

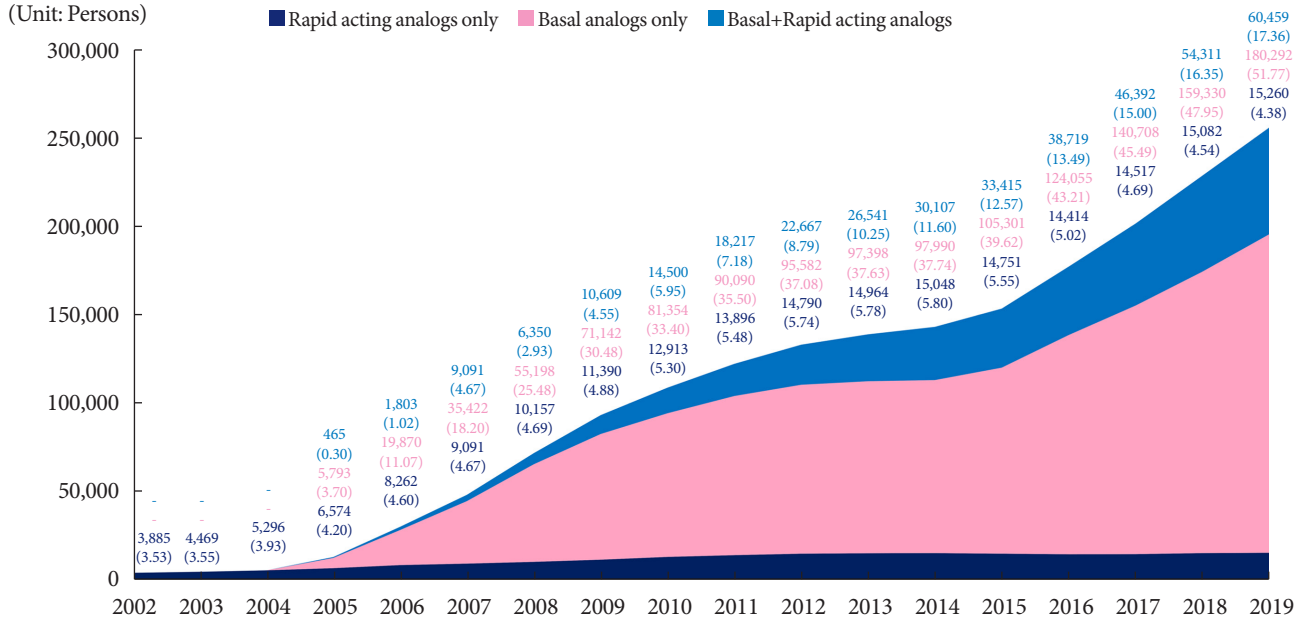

Fig. 2. Trends in rapid acting analogs and/or basal analogs use in type 2 diabetes mellitus.

on the types of antidiabetic drug that patients take in addition to insulin. Among insulin users in T2DM in 2019, 63,370 (18.2%) patients took one antidiabetic drug in addition to insulin. Metformin use increased steadily until 2014, and it continued to decrease until 2019. The use of DPP-4 inhibitor and SGLT2 inhibitor showed a steady increase since the start of the prescription availability. Trends of dual combinations of antidiabetic medication in insulin users from 2002 to 2010 and from 2011 to 2019 are indicated in Supplementary Tables 6 and 7, respectively. Among the dual combinations, the 14 com-

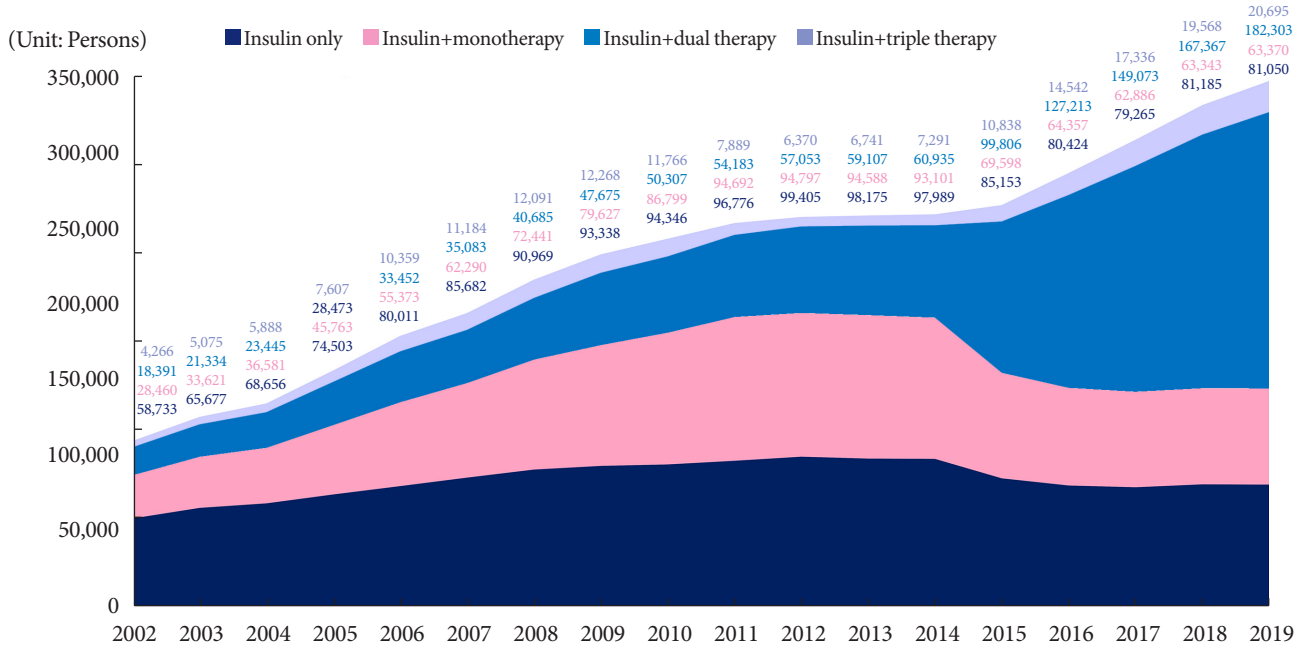

Fig. 3. Trends in antidiabetic medications use in addition to insulin in type 2 diabetes mellitus.

Table 2. Trends of monotherapy of antidiabetic agents among insulin users with type 2 diabetes mellitus from 2002 to 2019

	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
Insulin only	58,733 (53.41)	65,677 (52.19)	68,656 (50.96)	74,503 (47.58)	80,011 (44.56)	85,682 (44.01)	90,969 (41.99)	93,338 (39.99)	94,346 (38.73)	96,776 (38.14)	99,405 (38.56)	98,175 (37.93)	97,989 (37.74)	85,153 (32.04)	80,424 (28.01)	79,265 (25.63)	81,185 (24.43)	81,050 (23.27)
Metformin	9,193 (8.36)	12,772 (10.15)	14,728 (10.93)	17,879 (11.42)	20,778 (11.57)	25,367 (13.03)	31,059 (14.34)	38,244 (16.39)	43,471 (17.85)	50,408 (19.86)	52,711 (20.45)	53,617 (20.72)	52,978 (20.41)	32,693 (12.3)	26,686 (9.3)	24,619 (7.96)	24,224 (7.29)	23,565 (6.77)
SU	11,411 (10.38)	11,965 (9.51)	11,967 (8.88)	14,437 (9.22)	16,419 (9.14)	16,853 (8.66)	18,811 (8.68)	18,267 (7.83)	17,233 (7.07)	16,607 (6.54)	15,349 (5.95)	14,845 (5.74)	14,962 (5.76)	8,559 (3.22)	6,520 (2.27)	5,760 (1.86)	5,118 (1.54)	4,564 (1.31)
DPP-4i	-	-	-	-	-	-	-	143 (0.06)	158 (0.06)	358 (0.14)	918 (0.36)	1,180 (0.46)	1,254 (0.48)	14,991 (5.64)	20,358 (7.09)	22,520 (7.28)	24,460 (7.36)	26,109 (7.50)
SGLT2i	-	-	-	-	-	-	-	-	-	-	-	-	55 (0.02)	1,498 (0.56)	2,098 (0.73)	2,383 (0.77)	2,549 (0.77)	2,891 (0.83)
TZD	1,237 (1.12)	551 (0.44)	1,228 (0.91)	2,123 (1.36)	2,951 (1.64)	2,481 (1.27)	2,406 (1.11)	2,939 (1.26)	2,724 (1.12)	2,190 (0.86)	2,729 (1.06)	4,888 (1.89)	6,390 (2.46)	3,324 (1.25)	2,504 (0.87)	2,248 (0.73)	2,019 (0.61)	1,844 (0.53)
Meglitinide	217 (0.20)	435 (0.35)	732 (0.54)	2,305 (1.47)	4,948 (2.76)	7,358 (3.78)	8,172 (3.77)	7,513 (3.22)	10,903 (4.48)	12,614 (4.97)	12,102 (4.69)	10,956 (4.23)	9,644 (3.71)	4,538 (1.71)	3,192 (1.11)	2,509 (0.81)	1,912 (0.58)	1,500 (0.43)
AGI	6,402 (5.82)	7,898 (6.28)	7,926 (5.88)	9,019 (5.76)	10,277 (5.72)	10,231 (5.26)	11,983 (5.53)	12,521 (5.36)	12,309 (5.05)	12,512 (4.93)	10,986 (4.26)	9,096 (3.51)	7,818 (3.01)	3,937 (1.48)	2,746 (0.96)	2,402 (0.78)	2,067 (0.62)	1,639 (0.47)
GLP-1 RA	-	-	-	-	-	-	-	-	1 (<0.01)	3 (<0.01)	2 (<0.01)	6 (<0.01)	-	58 (0.02)	253 (0.09)	445 (0.14)	994 (0.30)	1,258 (0.36)

Values are presented as number (%).
SU, sulfonylurea; DPP-4i, dipeptidyl peptidase-4 inhibitor; SGLT2i, sodium glucose cotransporter 2 inhibitor; TZD, thiazolidinedione; AGI, alpha glucosidase inhibitor; GLP-1 RA, glucagon-like peptide-1 receptor agonist.

binations with the highest number of prescriptions are shown in these tables. The number of patients using DPP-4 inhibitor, SGLT2 inhibitor, and GLP1-RA in addition to insulin and metformin continues to increase. In 2019, the number of patients who were taking two an tidiabetic drugs in addition to insulin was 182,303 (52.4%) among total insulin users in T2DM; patients who took metformin plus DPP-4 inhibitor in addition to insulin increased to 26.1% (Supplementary Table 7). Supplementary Table 8 shows each antidiabetic medication included in the triple combination in addition to insulin. The

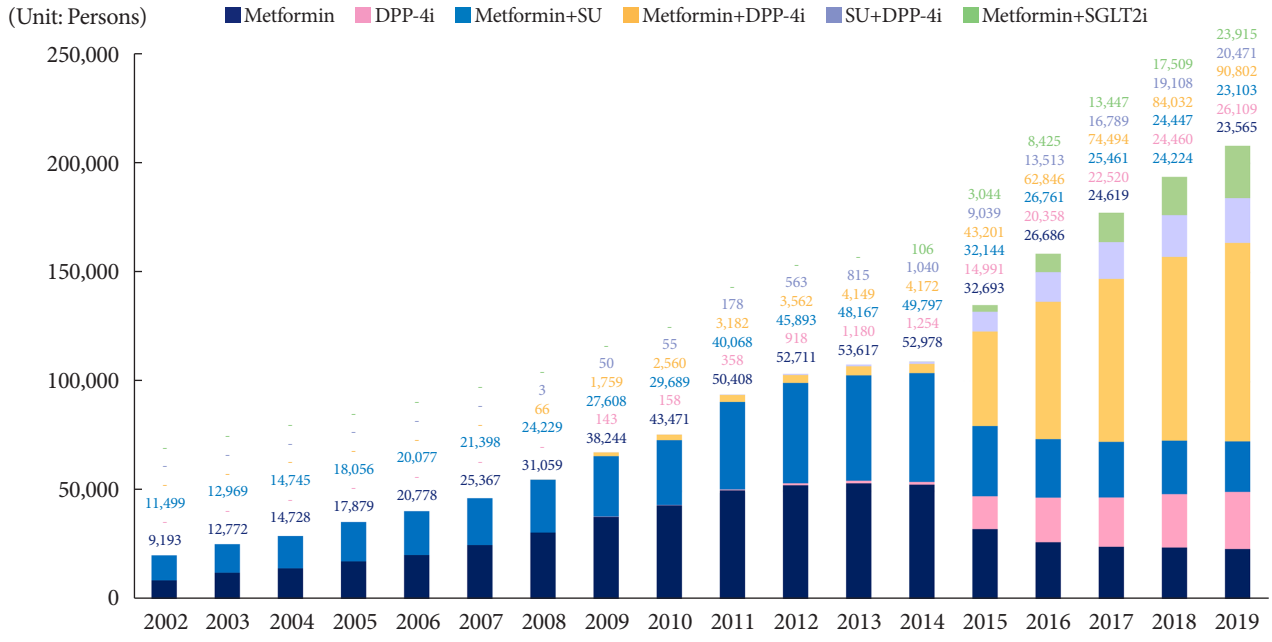

Fig. 4. Prescription trends in the six most commonly used antidiabetic medication in 2019 from 2002 to 2019. DPP-4i, dipeptidyl peptidase-4 inhibitor; SU, sulfonylurea; SGLT2i, sodium glucose cotransporter 2 inhibitor.

number of patients with T2DM who took three types of antidiabetic medication other than insulin was 20,695 (5.9%) in 2019. Among them, 96.3% took metformin, 84.8% took sulfonylurea, and 83.0% took DPP-4 inhibitors. The trends of the six most prescribed single or dual combination of antidiabetic drug in 2019 from 2002 to 2019 are shown in Fig. 4. The use of metformin monotherapy and metformin plus sulfonylurea increased but has decreased since 2015. The use of metformin plus DPP-4 inhibitor has markedly increased since 2015. The use of metformin plus SGLT2 inhibitor has also increased steadily since 2015.

DISCUSSION

The number of insulin users with T2DM has continued to increase since 2002. Among insulin users, the proportion of patients who use basal analogs has increased rapidly, reaching 75.1% of total insulin users with T2DM in 2019. In addition, the proportion of patients who use multiple daily injections, which is considered an intensified insulin regimen, has increased steadily. Among insulin users with T2DM, the use of antidiabetic medications other than insulin continues to increase, and the proportion of patients receiving dual therapy in addition to insulin is especially increasing. The most common dual combination therapy is metformin plus DPP-4 inhibitors, reaching 26.1% of total insulin users in 2019, followed by metformin plus SGLT2 inhibitor and metformin plus sulfonylurea. Considering that the use of metformin plus sulfonylurea accounted for up to 19.2% of patients in 2014, the use of this combination is decreasing, while the use of DPP-4 inhibitor and SGLT2 inhibitor is increasing. In addition, the use of metformin plus GLP-1 RA is increasing. This trend is because sulfonylurea is associated with issues of hypoglycemia or weight gain, while SGLT2 inhibitor and GLP-1 RA have acceptable profiles with significant cardiovascular and renal benefit when used alone and with a weight loss effect in addition to insulin [2]. DPP-4 inhibitor use is rapidly and widely growing because it seems to be beneficial regarding glycemic control without significant adverse effects [8].

The proportion of patients with T1DM using basal analogs or rapid acting analogs increased, while the proportion of those patients using human insulin, BHI or premixed insulin decreased. In this study, the numbers of insulin users with T1DM were 34,972 in 2002, 46,011 in 2009, and 20,287 in 2019. The patients who were prescribed insulin and claiming both T1DM and T2DM were 5,117 in 2002, 8,959 in 2009, and 12,102 in 2019. The number of patients prescribed insulin for T1DM alone has decreased, and the number of patients prescribed in-

sulin for both T1DM and T2DM has increased. In July 2011, the Korean NHIS promoted the T1DM registration so that registered patients could receive financial aid for consumable materials. After that, the patients with atypical T1DM which is defined as the T1DM with slowly progressive nature including latent autoimmune disease or long standing T2DM with insulin dependency increased in 2013, especially in age over 60 years [9]. Therefore, some insulin-using T2DM might be overestimated as T1DM. However, from around 2017, oral antidiabetic drug prescribed with the E10 ICD code are no longer covered by insurance, after that the proportion of T1DM might be underestimated. Song et al. [10] reported that the number of patients with T1DM from 2011 to 2013 using NHI data was 44,747 based on those who received insulin prescriptions three or more times. In the report, 85,764 patients were prescribed insulin at least once over the 2 years and 141,516 did not receive insulin prescription were among those claimed for T1DM [10]. In the Health Insurance Review & Assessment Service data, the numbers of patients with T1DM were 77,794 in 2017, 48,240 in 2019, and 44,827 in 2021 (opendata.hira.or.kr). These numbers were estimated through all claims claimed with primary ICD-10 code with E10 not confined to insulin claims. Therefore, the estimated numbers may have been overestimated when T1DM is defined by ICD-10 code alone. Therefore, in our study, we used a strict definition of T1DM that excluded patients who prescribed insulin during hospitalization and was limited to insulin users claiming T1DM alone to provide more accurate results. It is not easy to distinguish the types of diabetes in adults worldwide since T1DM has historically been characterized as having an onset during childhood [11], especially in Asia, the immunologic features and epidemiology of T1DM vary considerably compared to Caucasians, therefore, distinguishing type of diabetes even young patients is challenging [12]. In particular, it is estimated that the number of T1DM diagnoses could be affected by insurance policies in Korea. The purpose of this study was to analyze the trends in change of insulin only in cases where T1DM is certain (excluding group with overlapping T1DM and T2DM) rather than changes in the prevalence of T1DM [13].

According to diabetes factsheet published in 2022 by KDA, the number of patients being treated for T2DM was 3,900,596 in 2019. Among them, proportion of insulin users were 8.4%. In our study, the number of insulin user with T2DM was 348,254 in 2019. This number is close to the value reported in factsheet considering the definition of insulin users was more stringent in our study. In United States, 21.6% use insulin among patients with T2DM using antidiabetic medication in 2012 and in Japan, 17.9% use insulin in 2014 to 2016 [14,15]. The proportion of insulin user in T2DM is small compared to other counties. According to the reports regarding change in insulin prescription of T2DM in the United States, Japan, and Taiwan, analog insulin use largely has increased and premix insulin and human insulin use has decreased, similar to our study [16-19]. The proportion of long acting analog users was similar in each country: 65.5% in Japan (regardless of other insulin), 50% in United States (basal only), and 75% and 52% in Korea, regardless of other insulin and basal only. However, the proportion of basal plus bolus insulin use has remained constant in the United States, at about 40% among insulin users [18], while in Korea, the proportion using basal plus bolus insulin has increased steadily in T2DM but reaches only 17%. In contrast, among the patients using insulin with T2DM, the proportion of patients taking insulin only or insulin plus non-insulin monotherapy has decreased since 2014; the proportion of insulin plus non-insulin dual therapy has increased markedly since 2015 and has reached over 50% since 2018. This trend is similar to other studies reported in Japan [17] and Taiwan [16]. These studies reported that the patients using non-insulin drug in combination with insulin is much more prevalent than the patients using insulin alone, and the basal insulin only group or basal plus bolus group prefers to use non-insulin drug in combination with insulin than bolus only group. This is because combining other hypoglycemic agents with basal insulin is easier for patients to take and easier for physicians to educate than to intensify insulin therapy such as adding bolus insulin to basal insulin. In addition, intensified insulin therapy without proper education, multiple self-monitoring of glucose, or continuous glucose monitoring use might be associated with hypoglycemia, cardiovascular risk, and mortality in both T1DM and T2DM patients [20-23]. Considering that diabetes is progressive disease, patients with T2DM who need to use insulin might have decreased residual β-cell function. Without effective education on insulin dose control, continuous daily insulin dose titration by patients themselves is not effective. Additionally, inappropriate insulin dose adjustment could induce hypoglycemia and increase glycemic variability, which are associated with increased cardiovascular risk. Therefore, from a long-term perspective, an education system in the hospital supported by government policies that can support appropriate and intensified insulin administration when insulin

is needed is essential for the treatment of patients with DM and decreased residual β-cell function.

This study evaluated the insulin trends among insulin users with T1DM and T2DM. We also investigated the trends of antidiabetic drug use in T2DM insulin users from 2002 to 2019. A strength of this study is the use of the NHIS data, which encompasses almost all patients prescribed insulin in Korea. Therefore, we were able to assess the status of insulin use in almost the entire Korean population. A limitation of this study is that the diabetes classification is based on the ICD-10 code and outpatient insulin prescriptions; thus numbers for T1DM or T2DM patients may be overestimated or underestimated. In addition, we could not identify HbA1c and the status of glycemic control because the NHIS data set does not included this information. In the future, studies for the glycemic control status according to insulin type in insulin users with T1DM and T2DM or according to antidiabetic medication in insulin users with T2DM are needed.

In conclusion, this study identified important patterns of insulin use in Korea in T1DM and T2DM patients, including trends of predominant use of insulin and intensified insulin regimen. We also evaluated the antidiabetic medication trends in T2DM. Such knowledge will be informative for not only clinicians who treat diabetes but also health policy managers to manage diabetes in Korea.

SUPPLEMENTARY MATERIALS

Supplementary materials related to this article can be found online at https://doi.org/10.4093/dmj.2022.0346.

CONFLICTS OF INTEREST

Sang-Man Jin has been associate editor of the *Diabetes & Metabolism Journal* since 2022. He was not involved in the review process of this article. Otherwise, there was no conflict of interest.

AUTHOR CONTRIBUTIONS

Conception or design: J.P., G.K., J.H.K.
Acquisition, analysis, or interpretation of data: J.P., G.K., B. S.K., K.D.H., S.Y. K., S.H.P., Y.B.L., S.M.J., J.H.K.
Drafting the work: J.P., G.K.
Final approval of the manuscript: J.H.K.

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Supplementary Table 8. Trends in triple combination of antidiabetic agents among insulin users with type 2 diabetes mellitus from 2002 to 2019[a]

	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
Metformin	4,163 (97.59)	4,946 (97.46)	5,765 (97.91)	7,440 (97.8)	10,083 (97.34)	10,854 (97.05)	11,724 (96.96)	11,953 (97.43)	11,566 (98.3)	7,785 (98.68)	6,281 (98.6)	6,651 (98.66)	7,086 (97.19)	10,473 (96.63)	14,015 (96.38)	16,677 (96.2)	18,786 (96.00)	19,926 (96.28)
SU	4,191 (98.24)	4,974 (98.01)	5,770 (98.00)	7,437 (97.77)	10,031 (96.83)	10,727 (95.91)	11,554 (95.56)	11,612 (94.65)	11,152 (94.78)	7,500 (95.07)	6,043 (94.87)	6,389 (94.78)	6,674 (91.54)	9,597 (88.55)	12,592 (86.59)	14,884 (85.86)	16,643 (85.05)	17,557 (84.84)
DPP-4i	-	-	-	-	-	-	20 (0.17)	415 (3.38)	594 (5.05)	1,232 (15.62)	2,739 (43.00)	4,273 (63.39)	5,211 (71.47)	9,262 (85.46)	12,600 (86.65)	14,843 (85.62)	16,669 (85.18)	17,169 (82.96)
SGLT2i	-	-	-	-	-	-	-	-	-	-	-	-	68 (0.93)	272 (2.51)	795 (5.47)	1,459 (8.42)	1,757 (8.98)	2,614 (12.63)
TZD	464 (10.88)	491 (9.67)	490 (8.32)	656 (8.62)	857 (8.27)	680 (6.08)	900 (7.44)	847 (6.90)	656 (5.58)	500 (6.34)	552 (8.67)	681 (10.10)	1,220 (16.73)	1,809 (16.69)	2,538 (17.45)	2,940 (16.96)	3,512 (17.95)	3,593 (17.36)
Meglitinide	78 (1.83)	188 (3.70)	265 (4.50)	498 (6.55)	891 (8.60)	1,331 (11.90)	1,457 (12.05)	1,350 (11.00)	890 (7.56)	401 (5.08)	196 (3.08)	188 (2.79)	182 (2.5)	169 (1.56)	204 (1.40)	193 (1.11)	212 (1.08)	165 (0.8)
AGI	3,902 (91.47)	4,626 (91.15)	5,374 (91.27)	6,790 (89.26)	9,215 (88.96)	9,960 (89.06)	10,618 (87.82)	10,627 (86.62)	10,434 (88.68)	6,242 (79.12)	3,290 (51.65)	2,032 (30.14)	1,423 (19.52)	919 (8.48)	772 (5.31)	700 (4.04)	602 (3.08)	490 (2.37)
GLP-1 RA	-	-	-	-	-	-	-	-	6 (0.05)	7 (0.09)	9 (0.14)	9 (0.13)	9 (0.12)	13 (0.12)	110 (0.76)	312 (1.80)	523 (2.67)	571 (2.76)

Values are presented as number (%).
SU, sulfonylurea; DPP-4i, dipeptidyl peptidase-4 inhibitor; SGLT2i, sodium glucose cotransporter 2 inhibitor; TZD, thiazolidinedione; AGI, alpha glucosidase inhibitor; GLP-1 RA, glucagon-like peptide-1 receptor agonist.
[a]Each drug in the triple combination is listed separately.