• Clinical Research •

Sodium-glucose cotransporter-2 inhibitors and dipeptidyl peptidase-4 inhibitors on diabetic macular edema and the need for intravitreal injection

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Abstract

● **AIM:** To investigate the effects of dipeptidyl peptidase-4 inhibitors (DPP4i) and sodium-glucose cotransporter-2 inhibitors (SGLT2i) on diabetic macular edema (DME) and the need for intravitreal injections (IVT) in patients with type 2 diabetes.

● **METHODS:** Data were retrospectively collected from the medical records of patients with diabetic retinopathy (DR) taking either DPP4i or SGLT2i as secondary oral hypoglycemic agents in addition to metformin between January 2019 and July 2022. We compared the prevalence of DME and the need for IVT among patients treated with DPP4i or SGLT2i. Propensity score matching was performed using the following variables: age, duration of diabetes, blood glucose control (HbA1c) level, and severity of DR.

● **RESULTS:** A total of 268 patients with DR were included in this study. More DPP4i users needed IVT than SGLT2i users (35.3% *vs* 18.0%, *P*=0.011), while the prevalence of DME was not different. The use of SGLT2i was associated with a lower need for IVT than DPP4i [odds ratio (OR) 0.404, 95% confidence interval (CI) 0.198–0.823], and similar trends were observed after propensity score matching (OR 0.419, 95%CI 0.181–0.970). However, this tendency was not significant in multiple logistic regressions. For DME, the use of DPP4i was not a significant risk factor compared to SGLT2i.

● **CONCLUSION:** The use of SGLT2i may be associated with a lower need for IVT for overall DR complications, while other factors may contribute to this effect. The effect of SGLT2i on the prevention of DME is not evident.

● **KEYWORDS:** diabetic macular edema; diabetic retinopathy; dipeptidyl peptidase-4 inhibitor; intravitreal injection; sodium-glucose cotransporter-2 inhibitor
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INTRODUCTION

Several complications of diabetic retinopathy (DR) result in significant visual impairment. Diabetic macular edema (DME) is one of the main causes of central vision loss, which can occur at any stage of DR[1]. Before irreversible damage occurs, patients are usually treated with intravitreal injection (IVT) of anti-vascular endothelial growth factor (VEGF) agents or corticosteroids according to their ocular status to reduce the need for surgery and prevent further damage[2-3].

The use of dipeptidyl peptidase-4 inhibitors (DPP4i) and sodium-glucose cotransporter-2 inhibitors (SGLT2i) has steadily increased in Korea and has been added as a secondary medication to metformin[4]. These oral hypoglycemic agents may have additional effects on diabetic microvascular complications in addition to their glucose-lowering function. There are controversial reports on the effects of DPP4i on DR, ranging from DR aggravation to improvement[5-7]. SGLT2i seem to be protective to kidneys *via* both blood glucose-dependent and blood glucose-independent mechanisms[8]. As diabetic microvascular complications share common characteristics, the effect of SGLT2i on DR was also investigated in various studies reporting at least neutral or protective effects on DR progression[9-10].

We previously conducted a cohort study to compare the effects of DPP4i and SGLT2i on the occurrence and progression of DR, and the results showed a protective effect of SGLT2i in DR occurrence but no significant differences in DR

progression[11]. Similarly, other studies on the relationship between oral hypoglycemic agents and DR have mainly focused on DR progression[12]. Meanwhile, DME and other complications of DR requiring IVT, such as neovascularization and subsequent vitreous hemorrhage, might be more clinically significant and crucial for visual impairment. Therefore, it is worth studying the effects of hypoglycemic agents on DME and other complications of DR. Accordingly, we investigated the effects on these complications by comparing DPP4i users and SGLT2i users.

PARTICIPANTS AND METHODS

Ethical Approval This study complied with the Declaration of Helsinki and was approved by the Institutional Review Board of Ajou University Hospital, Suwon, Korea (IRB No.AJOUIRB-DB-2023-136). Informed consent was waived due to the retrospective nature of the study.

Study Design We retrospectively reviewed the medical records of DR patients who first visited the Ophthalmology Department of Ajou University Hospital between January 2019 and July 2022. The exclusion criteria were as follows: 1) patients with type 1 diabetes, 2) those who had no DR on fundus examination, 3) those who presented with retinal disorders other than DR, 4) those with a history of vitrectomy or focal/grid laser photocoagulation, 5) those without records of hypoglycemic medications, 6) those without glycated hemoglobin (HbA1c) data, 7) those who received IVT or panretinal photocoagulation within the last 6mo.

Among the patients initially recruited, those using DPP4i or SGLT2i in addition to metformin were identified in the study population. Demographic and clinical data were obtained from the medical records, including age, sex, history of hypertension or end-stage renal disease, duration of diabetes, and medications. The blood glucose control level (HbA1c) and serum lipid profiles were obtained within 3mo of initial encounter, and the values evaluated after IVT or the diagnosis of DME were not considered. Ocular treatment history, such as previous laser photocoagulation, IVT, and cataract surgery, and DR severity as nonproliferative DR or proliferative DR (PDR), were also obtained from medical records.

The primary outcome was the presence of DME, defined as a central retinal thickness ≥320 μm in men and ≥305 μm in women on optical coherence tomography (Spectralis®, Heidelberg Engineering, Heidelberg, Germany). Secondary outcomes were other complications of PDR, such as neovascularization, vitreous hemorrhage and neovascular glaucoma, and the need for IVT with anti-VEGF agents. The agents used in IVT consisted of bevacizumab, ranibizumab, aflibercept, triamcinolone, and dexamethasone implants. The decision to perform IVT was determined by one of the two retinal specialists (Chung YR and Lee K).

Statistical Analysis Statistical analyses were performed using SPSS Statistics software (version 25.0, IBM, Armonk, NY, USA). Decimal visual acuity data was logarithmically transformed into a logMAR scale, with corresponding values: counting fingers to 1.7, hand motion to 2.3, light perception to 2.4, and no light perception to 2.6. Categorical variables were compared using the Chi-square test, whereas continuous variables were compared using the independent *t*-test. Logistic regression analysis was performed to identify associated factors, and the results are presented as odds ratios (ORs) and 95% confidence intervals (CIs). Multivariate analysis in logistic regression was based on variables significant in univariate analysis. The time from the initiation of DPP4i or SGLT2i therapy to events was assessed using Kaplan-Meier plots and log-rank tests. Propensity score matching of DPP4i and SGLT2i users was based on age, duration of diabetes, HbA1c level, and DR severity. A P value <0.05 was considered statistically significant.

RESULTS

A total of 834 patients with diabetes were initially identified, and the final inclusion consisted of 207 patients as DPP4i users and 61 patients as SGLT2i users (Table 1). Most baseline characteristics were not significantly different between groups, including the duration of diabetes or degree of blood glucose control, except that more DPP4i users presented with PDR (34.8% *vs* 13.1%, P=0.001). This discrepancy was adjusted after propensity score matching (Table 1).

There were more patients who presented DME in DPP4i users without statistical significance (22.7% *vs* 14.8%, P=0.179), and this tendency was similar to that of matched patients (Table 2). However, there were more patients presenting neovascular complications (23.2% *vs* 8.2%, P=0.010) as well as more IVT performed in DPP4i users than in SGLT2i users (35.3% *vs* 18.0%, P=0.011). The different proportions that received IVT remained significant in matched patients (34.4% *vs* 18.0%, P=0.040). Notably, the agents used for IVT consisted of bevacizumab (81.0%), ranibizumab (1.2%), aflibercept (14.3%) and corticosteroids (3.6%), and there were no significant differences in the type of agents used to IVT (Table 2). No significant difference was observed in the amount of visual acuity change between DPP4i users and SGLT2i users.

Logistic regression analysis revealed that baseline visual acuity and PDR were the significant factors associated with a higher risk of DME in both unmatched and matched patients (Table 3). PDR remained significant factor in the multivariate analysis, only in the unmatched patients.

Meanwhile, the use of SGLT2i was associated with a lower risk of IVT (OR 0.404, 95%CI 0.198–0.823 for unmatched patients; OR 0.419, 95%CI 0.181–0.970 for matched patients; Table 4). Their statistical significance disappeared in

Table 1 Baseline characteristics of included patients mean±SD or *n* (%)

Variables	Unmatched patients			Matched patients		
	DPP4i (*n*=207)	SGLT2i (*n*=61)	*P*	DPP4i (*n*=61)	SGLT2i (*n*=61)	*P*
Age (y)	58.1±11.4	55.9±9.5	0.169	57.9±12.4	55.9±9.5	0.302
Sex (male)	133 (64.3)	47 (77.0)	0.061	41 (67.2)	47 (77.0)	0.226
Duration of diabetes (y)	12.7±9.5	10.8±8.9	0.164	11.0±8.4	10.8±8.9	0.921
Hypertension	94 (45.4)	26 (42.6)	0.700	26 (42.6)	26 (42.6)	1.000
End-stage renal disease	3 (1.4)	0	0.344	1 (1.6)	0	0.344
Previous PRP	15 (7.2)	1 (1.6)	0.104	1 (1.6)	1 (1.6)	1.000
Previous injection	10 (4.8)	0	0.080	3 (4.9)	0	0.079
Pseudophakia	30 (14.5)	7 (11.5)	0.548	7 (11.5)	7 (11.5)	1.000
DR state (PDR)	72 (34.8)	8 (13.1)	0.001[a]	13 (21.3)	8 (13.1)	0.230
Baseline BCVA (logMAR)	0.45±0.46	0.33±0.40	0.051	0.48±0.47	0.33±0.40	0.049[a]
HbA1c (%)	7.9±1.7	8.0±1.2	0.715	8.0±1.7	8.0±1.2	0.995
Total cholesterol (mg/dL)	156.9±46.7	147.8±37.8	0.172	159.2±56.1	147.8±37.8	0.202
Triglycerides (mg/dL)	152.1±108.2	136.0±57.0	0.175	164.3±138.8	136.0±57.0	0.214
HDL cholesterol (mg/dL)	48.3±12.9	48.5±10.2	0.906	48.1±12.3	48.5±10.2	0.837
LDL cholesterol (mg/dL)	80.7±36.6	72.9±31.2	0.162	83.2±44.3	72.9±31.2	0.174

[a]*P*<0.05 by independent *t* test. BCVA: Best-corrected visual acuity; DPP4i: Dipeptidyl peptidase-4 inhibitor; DR: Diabetic retinopathy; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; PDR: Proliferative diabetic retinopathy; PRP: Panretinal photocoagulation; SGLT2i: Sodium-glucose cotransporter-2 inhibitor; HbA1c: Glycated hemoglobin.

Table 2 Ocular outcomes of included patients mean±SD or *n* (%)

Variables	Unmatched patients			Matched patients		
	DPP4i (*n*=207)	SGLT2i (*n*=61)	*P*	DPP4i (*n*=61)	SGLT2i (*n*=61)	*P*
Change of BCVA (logMAR)	0.10±0.37	0.05±0.33	0.349	0.05±0.39	0.05±0.33	0.977
DME	47 (22.7)	9 (14.8)	0.179	16 (26.2)	9 (14.8)	0.116
NV/vitreous hemorrhage	48 (23.2)	5 (8.2)	0.010[a]	9 (14.8)	5 (8.2)	0.256
IVT	73 (35.3)	11 (18.0)	0.011[a]	21 (34.4)	11 (18.0)	0.040[a]
Agents used in IVT			0.145			0.151
Bevacizumab	61	7		18	7	
Ranibizumab	1	0		0	0	
Aflibercept	8	4		3	4	
Triamcinolone/dexamethasone	3	0		0	0	

[a]*P*<0.05 by Chi-square test. BCVA: Best-corrected visual acuity; DPP4i: Dipeptidyl peptidase-4 inhibitor; NV: Neovascularization of the iris of retina; IVT: Intravitreal injection; SGLT2i: Sodium-glucose cotransporter-2 inhibitor; DME: Diabetic macular edema.

multivariate logistic regression, while DR severity remained a risk factor for IVT (Table 4).

The time from initiation of medication to DME was not significantly different between DPP4i users and SGLT2i users (unmatched patients, log-rank *P*=0.441; Figure 1A) or in matched patients (log-rank *P*=0.301). A similar tendency was found for IVT for both unmatched patients (log-rank *P*=0.118; Figure 1B) and matched patients (log-rank *P*=0.292).

DISCUSSION

Metformin is an oral hypoglycemic agent that is commonly used as a first-line therapy in Korea as well as other countries, while DPP4i and SGLT2i are often prescribed as secondary medications added to metformin[4]. Several studies have compared the effects of DPP4i and SGLT2i in the macrovascular complications of DR, as both medications seem to reduce the risk of cardiovascular diseases in addition to their hypoglycemic effect[13]. One report found no significant differences in venous thromboembolism[14], while a more reduced risk for major adverse cardiovascular events and heart failure was noted with the use of SGLT2i compared to DPP4i[15-16]. In some countries, SGLT2i are replacing DPP4i and sulfonylureas, probably due to their additional protective effect on cardiovascular and renal disorders[17]. The difference in cohort size between DPP4i users and SGLT2i users might be related to the current prescription tendency in Korea: DPP4i (approved in 2008) is the second most popular antidiabetic medication after metformin in Korea since 2015, while SGLT2i was approved only in 2014[4]. The male predominance

Table 3 Logistic regression for factors associated with DME

Variables	Unmatched patients						Matched patients					
	Univariate analysis			Multivariate analysis[b]			Univariate analysis			Multivariate analysis[b]		
	OR	95%CI	*P*	OR	95%CI	*P*	OR	95%CI	*P*	OR	95%CI	*P*
Age	0.978	0.951–1.005	0.105				0.996	0.957–1.036	0.834			
Sex (male)	0.699	0.380–1.286	0.249				0.493	0.196–1.242	0.134			
Duration of diabetes	0.994	0.963–1.027	0.724				1.013	0.963–1.065	0.622			
Hypertension	0.564	0.605–1.044	0.068				0.567	0.224–1.437	0.232			
Baseline BCVA	2.688	1.468–4.920	0.001[a]	1.806	0.937–3.481	0.078	2.926	1.168–7.330	0.022[a]	2.205	0.762–6.378	0.145
DR state (PDR)	3.738	2.024–6.904	<0.001[a]	3.022	1.562–5.844	0.001[a]	3.041	1.093–8.461	0.033[a]	1.921	0.575–6.420	0.289
Previous PRP	2.424	0.841–6.985	0.101				0.000	0.000–NA[c]	0.999			
Hypoglycemic agent (SGLT2i)	0.589	0.270–1.284	0.183				0.487	0.196–1.208	0.121			
HbA1c	1.050	0.879–1.255	0.589				1.036	0.773–1.388	0.813			

[a]*P*<0.05 by logistic regression analysis; [b]Variables with *P*<0.05 in the univariate analysis were included in the multivariate analysis; [c]Results related to low incidences of previous PRP cases in matched patients (one case in each group, Table 1). OR: Odds ratio; CI: Confidence interval; DME: Diabetic macular edema; BCVA: Best-corrected visual acuity; DR: Diabetic retinopathy; PDR: Proliferative diabetic retinopathy; PRP: Panretinal photocoagulation; SGLT2i: Sodium-glucose cotransporter-2 inhibitor; HbA1c: Glycated hemoglobin.

Table 4 Logistic regression for factors associated with IVT

Variables	Unmatched patients						Matched patients					
	Univariate analysis			Multivariate analysis[b]			Univariate analysis			Multivariate analysis[b]		
	OR	95%CI	*P*	OR	95%CI	*P*	OR	95%CI	*P*	OR	95%CI	*P*
Age	0.970	0.947–0.994	0.016[a]	0.999	0.968–1.032	0.963	0.996	0.961–1.033	0.844			
Sex (male)	0.654	0.381–1.122	0.123				0.445	0.189–1.049	0.064			
Clinician	0.674	0.390–1.164	0.157				0.562	0.242–13306	0.180			
Duration of diabetes	0.995	0.967–1.023	0.704				1.003	0.957–1.051	0.904			
Hypertension	0.783	0.464–1.320	0.359				0.750	0.328–1.716	0.496			
Baseline BCVA	4.885	2.554–9.344	<0.001[a]	2.077	0.649–4.563	0.069	7.729	2.545–23.468	<0.001[a]	3.114	0.914–10.609	0.069
DR state (PDR)	20.625	10.629–40.021	<0.001[a]	18.429	8.291–40.961	<0.001[a]	12.353	4.192–36.403	<0.001[a]	7.173	2.146–23.973	0.001[a]
Previous PRP	4.009	1.406–11.431	0.009[a]	0.303	0.160–1.770	0.303	2.871	0.174–47.296	0.461			
Hypoglycemic agent (SGLT2i)	0.404	0.198–0.823	0.013[a]	0.729	0.299–1.771	0.484	0.419	0.181–0.970	0.042[a]	0.507	0.192–1.336	0.169
HbA1c	1.002	0.855–1.175	0.980				0.997	0.759–1.312	0.986			

[a]*P*<0.05 by logistic regression analysis. [b]Variables with *P*<0.05 in the univariate analysis were included in the multivariate analysis. OR: Odds ratio; CI: Confidence interval; IVT: Intravitreal injection; BCVA: Best-corrected visual acuity; DR: Diabetic retinopathy; PDR: Proliferative diabetic retinopathy; PRP: Panretinal photocoagulation; SGLT2i: Sodium-glucose cotransporter-2 inhibitor; HbA1c: Glycated hemoglobin.

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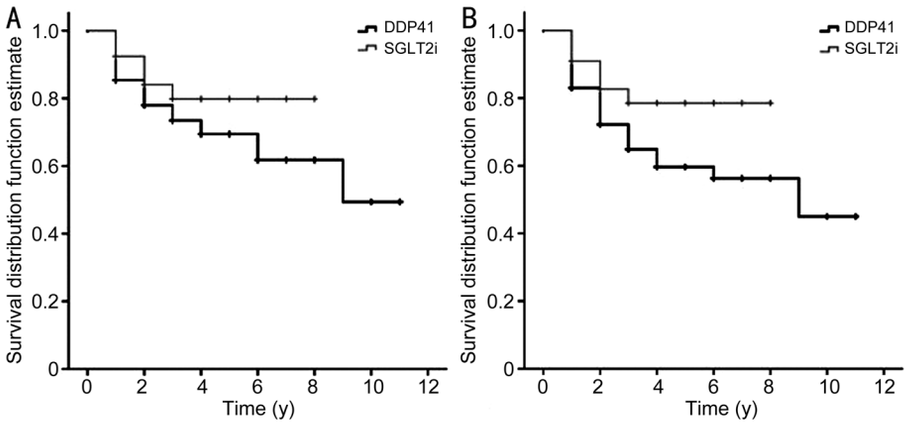

Figure 1 Kaplan-Meier survival curves A: The time from initiation of medication to diabetic macular edema (DME) was not significantly different between dipeptidyl peptidase-4 inhibitor (DPP4i) users and sodium-glucose cotransporter-2 inhibitors (SGLT2i) users (log-rank *P*=0.441); B: The time to intravitreal injection (IVT) was neither significantly different between DPP4i users and SGLT2i users (log-rank *P*=0.118).

in both DPP4i users and SGLT2i users should be related to the characteristic of the Korean diabetic population in which the prevalence of diabetes was higher in men[4].

Diabetic nephropathy and DR are representative microvascular complications of diabetes sharing common pathogenesis[18]. A renoprotective effect slowing the progression of established chronic kidney disease was reported with SGLT2i, resulting in the recommendation of SGLT2i for patients with diabetes[19-20]. SGLT2i seem to improve glomerular hyperfiltration and reduce renal oxygen consumption and inflammatory reactions beyond the glucose-lowering effect[21]. These mechanisms might be applied similarly in DR. A recent cohort study comparing hypoglycemic agents for the risk of DR found that SGLT2i users had a lower risk of developing DR than DPP4i, glucagon-like peptide-1 receptor agonist, or insulin users[22]. This was similar to our previous results, showing a lower risk of DR occurrence in SGLT2i users than in DPP4i users[11].

In this study, fewer SGLT2i users presented neovascular complications of DR and needed IVT for DR complications than DPP4i users. This might be in concordance with reduced frequency of IVT with anti-VEGF agents reported with SGLT2i users in a recent Japanese cohort study (to note, they did not include bevacizumab)[23]. The use of DPP4i was associated with a higher risk of IVT-requiring situations in DR patients compared to SGLT2i, while there was no specific association with DME. Although DR is an important complication of diabetes, its presence itself does not always require immediate ocular treatment. Patients with nonproliferative DR are often followed up regularly until progression to PDR stage or the development of DME that requires treatment occurs. Neovascularization in DR, the hallmark of PDR, is traditionally treated by panretinal photocoagulation; however, anti-VEGF agents are now widely used with benefits in preserving peripheral visual fields[2]. The larger proportion of patients presenting active neovascular complications in DPP4i users should be related to a higher rate of PDR, as the difference was not significant after matching. Less need for IVT in patients with DR can achieve a reduced treatment burden for both patients and clinicians. Although IVT was still less needed in SGLT2i users than DPP4i users even after propensity score matching, it should be noted that this tendency was no longer significant when adjusted with other factors. The fact that the lower risk of IVT in SGLT2i users compared to DPP4i users was not significant in multivariate analysis suggests that other factors such as DR severity may be contributing. PDR was still an important factor for IVT in matched patients, suggesting that the risk related to IVT may be due to the presence of PDR, not necessarily DME. The loss of statistical significance of previous PRP as a risk factor in IVT may also explain the effect of PDR, as PRP is still an important treatment modality in PDR patients. On the other hand, various regimens regarding IVT frequency have been introduced and treat-to-extend regimen seems to apply more frequent injections than pro-re-nata regimen[24]. As each clinician may have a preferred IVT regimen, we verified the effect of clinician's factor in IVT and found that it was not significant when considered with other potential factors.

DME develops *via* dysregulation of the blood-retinal barrier and glial dysfunction, which results in the accumulation of fluid in the subretinal or intraretinal spaces of the macula[25]. Inflammation and ischemia also contribute to the development of DME, resulting in IVT with anti-VEGF agents or corticosteroids being widely used for treatment[25]. Although IVT has been an effective treatment modality in DME, its frequent administration may result in treatment burden as well as an increased possibility of ocular complications such as endophthalmitis and retinal detachment. We investigated whether the use of SGLT2i reduces the risk of DME, which was not evident in this study. This was similar to a recent Japanese cohort study that showed no difference in the risk

ratios for DME events between SGLT2i users and non-users[23]. The prevalence of DME, which is a complication that can occur at any stage of DR, did not differ according to the type of hypoglycemic medication used.

The major limitations of this study rely on the relatively small number of patients and the retrospective nature. The decision to perform IVT was based on each ophthalmologist's choice; therefore, the effect of selection bias could not be excluded. Although the clinician's factor was not significant in multiple regression analysis, the different preference of IVT regimen in DR patient should be considered. As IVT was determined as its initial application, the lack of data on frequency or total number of IVT is another limitation of this study. Hypertension was defined by its presence *via* medical records, not by actual blood pressure values. Considering that blood pressures are suggested to affect the development of DME[26-27], these factors should be also considered in further studies. The laboratory data including HbA1c level and serum lipid profiles were limited to those obtained within 3mo of initial encounter and closest to the event when applicable, while considering these factors as time-dependent variables in further longitudinal studies may provide information on their impact in DME or the need of IVT. Functional parameters were not considered as outcomes, as it was challenging to isolate the effects of DPP4i and SGLT2i on visual function in this retrospective study.

Despite the abovementioned limitations, this study has the following strengths: 1) the inclusion of bevacizumab, whose data are often unavailable owing to its off-label use in most countries; 2) identification of each patient's glycemic control; 3) additional propensity score-matched analysis using factors that affect DR. It should be noted that the severity of DR, *i.e.* the presence of PDR was always a significant factor for the risk of IVT-requiring complications, although propensity score matching was performed.

In conclusion, this study suggests the potency of SGLT2i in reducing IVT-requiring situations in patients with DR was not significant when considered with other contributing factors such as DR severity. Among IVT-requiring DR complications, DME was not affected by the type of oral hypoglycemic agents. Physicians might consider various factors when selecting hypoglycemic agents for patients with type 2 diabetes. Further prospective studies with larger patient populations are needed to better understand the effect of SGLT2i on DR complications and visual function.

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