

# World Journal of *Clinical Cases*

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## Observational Study

## Impacts of statin and metformin on neuropathy in patients with type 2 diabetes mellitus: Korean Health Insurance data

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**Author contributions:** Min HK and Kim SH designed the research study; Min HK, Kim SH, Choi JH, Choi K and Kim HR performed the research; Min HK contributed analytic tools; Min HK analyzed the data and wrote the manuscript; all authors have read and approve the final manuscript.

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**Informed consent statement:** The HIRA database is accessible to all researchers and holds anonymized patient information to protect the privacy of individuals. The HIRA database can be accessed by any researchers whose study protocols have been approved by an official review committee, and Informed consent of HIRA data is omitted. Therefore, written informed consent for enrollment was waived because the data were provided by HIRA.

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## Abstract

## BACKGROUND

Neuropathy is a common chronic complication in type 2 diabetes mellitus (T2DM). Statin and metformin are commonly used medications in T2DM patients, and some studies showed statin- or metformin-induced neuropathy.

## AIM

To evaluate the incidence of neuropathy among patients with T2DM associated with statin and metformin therapies.

## METHODS

Korean Health Insurance Review and Assessment national patient sample data from 2016 and 2017 were used. Patients with T2DM and no complications were divided into statin/metformin/statin + metformin users and non-users. Neuropathy incidence was defined by International Statistical Classification of Diseases and Related Health Problems, 10<sup>th</sup> revision codes and concomitant prescriptions for anticonvulsants or antidepressants. Logistic regression analyses were conducted to examine the associations between statin/metformin/statin + metformin therapies and the incidence of neuropathy. Propensity score (PS) matching was performed on the basis of age, sex and comorbidities.

## RESULTS

Overall, 34964 and 35887 patients with T2DM and no complications were included in the Korean Health Insurance Review and Assessment national patient sample datasets from 2016 and 2017, respectively. Statin therapy was associated



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with increased risks of neuropathy in 2016 and 2017 [PS-matched odds ratio (OR) = 1.22, 95% confidence interval (CI): 1.08-1.38; PS-matched OR = 1.17, 95% CI: 1.03-1.33, respectively]. Metformin therapy was associated with reduced risks of neuropathy in 2016 and 2017 (PS-matched OR = 0.30, 95% CI: 0.21-0.42; PS-matched OR = 0.44, 95% CI: 0.32-0.60, respectively). Combined statin + metformin therapy was not significantly associated with neuropathy in 2016 or 2017 (PS-matched OR = 0.85, 95% CI: 0.61-1.19; PS-matched OR = 0.95, 95% CI: 0.66-1.38, respectively).

## CONCLUSION

Statin therapy was associated with enhanced risk of new-onset neuropathy in patients with T2DM, but metformin therapy showed the opposite association.

**Key Words:** Diabetes mellitus; Neuropathies; Hydroxymethylglutaryl-CoA reductase inhibitors; Metformin

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**Core Tip:** Diabetic neuropathy is one of the most common chronic complications in patients with type 2 diabetes mellitus. Statin is a commonly used lipid lowering agent in patients with type 2 diabetes mellitus, and metformin is background medication for type 2 diabetes mellitus. In some observational studies, statin and metformin were associated with an increased risk of neuropathy. In the present study using Korean Health Insurance Review and Assessment national patient sample data, the use of statin was associated with increased risk of diabetic neuropathy occurrence, whereas metformin use showed a negative association with diabetic neuropathy.

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## INTRODUCTION

The prevalence of type 2 diabetes mellitus (T2DM) and dyslipidemia are increasing with increased population aging worldwide[1,2]. These two diseases are related to cardiovascular disease (CVD), such that they result in higher incidences of CVD-related morbidities and mortalities. Therefore, the proper management of T2DM and dyslipidemia is important for preventing CVD[3,4]. Furthermore, the treatment targets for dyslipidemia differ among comorbidities, and patients with very high risks of CVD are recommended to have low-density lipoprotein-cholesterol levels below 70 mg/dL [3]. Several major risk factors for CVD are known, including dysglycemia (*e.g.*, T2DM) [3]. In practice, statins (*i.e.* hydroxymethylglutaryl-CoA reductase inhibitors) are used as first-line therapy for dyslipidemia[3]. Despite their broad usage, some studies have shown that statins may induce neuropathy[5,6].

Metformin, a biguanide, is a first-line oral medication for patients with T2DM that can reduce hepatic glucose production and intestinal glucose absorption, but it also enhances insulin sensitivity[4]. In addition to its primary therapeutic effects, metformin has demonstrated anti-inflammatory effects through the modulation of the AMPK/mTOR pathway[7]. Furthermore, metformin does not induce hypoglycemia, which is a critical side effect of other anti-diabetic drugs. Although metformin is commonly used as a background medication in patients with T2DM[4,8], a potential risk for metformin-induced neuropathy has recently been proposed. Patients with T2DM and neuropathy reportedly have lower vitamin B12 levels, and a higher metformin dose is associated with lower vitamin B12 levels[9]. However, the association between metformin and diabetic neuropathy remains controversial[10].

Dyslipidemia in patients with T2DM is more severe in terms of inducing atherosclerosis, high triglyceride levels, reduced high-density lipoprotein-cholesterol levels



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and elevated low-density lipoprotein-cholesterol levels[11]. Furthermore, there are shared risk factors (e.g., old age and obesity) between T2DM and dyslipidemia[12,13]. Therefore, the use of anti-diabetic medications and statins in both groups of patients are common situations in clinical practice. In addition, neuropathy is a chronic microvascular complication in patients with T2DM that depends on the duration and severity of T2DM. Therefore, primary prevention *via* proper glycemic control is important[12]. In addition, the avoidance of additional risk of neuropathy is an important consideration. However, little is known regarding the impact of commonly used medications, *i.e.* statins and metformin, on neuropathy development in patients with T2DM.

The Korean health insurance system covers the entire population of residents in Korea. All health care facilities provide medical services to patients, then submit insurance benefit claims to the national health insurance service. These insurance claims are collected in the Health Insurance Review and Assessment (HIRA) database, which is used annually to produce representative sample data comprising approximately 3% of all insurance claims, the HIRA national patient sample (NPS). HIRA-NPS data are useful for analyzing various medical insurance-related data including treatments, procedures, prescriptions, patient demographics and health care provider information. Furthermore, these data can be used to analyze the incidences of specific disorders based on operational definitions.

In the present study, we evaluated the influence of statin, metformin and statin + metformin therapies on the incidence of neuropathy in patients with T2DM using Korean HIRA-NPS data from 2016 and 2017.

## MATERIALS AND METHODS

### Data sources

Korean HIRA-NPS data are produced annually, and this study included HIRA-NPS data from 2016 and 2017. Korea has a unique government-funded insurance system, in which claims data are generated when healthcare facilities file insurance benefit claims with HIRA. These claims data include diverse information such as patient demographics; detailed information concerning treatments, costs, prescriptions and healthcare provider information. The Korean HIRA annually provides sample data, the NPS, by randomly extracting nationwide health insurance claims data using a sampling strategy stratified according to sex and age. Each HIRA-NPS dataset includes data collected for the entire index year. Approximately 3% of all covered patients, approximately 1.45 million individuals, are selected for inclusion in the sample, and their personal information is anonymized. Therefore, HIRA-NPS claims data represent real-world clinical circumstances that occur throughout Korea.

This study was conducted in accordance with the tenets of the Declaration of Helsinki (1964). Written informed consent for enrollment was waived because the data were provided by HIRA. This study was approved by the Institutional Review Board of Konkuk University Medical Center (Approval number: 2020-12-057).

### Data extraction

Considering the characteristics of HIRA-NPS data, operational definitions of T2DM and new-onset neuropathy were used in this study. Patients were selected based on the International Statistical Classification of Diseases and Related Health Problems, 10<sup>th</sup> revision (ICD-10). At baseline, ICD-10 codes for T2DM without chronic complications were selected by searching for the following ICD-10 codes: E110, E111, E119, E120, E121, E129, E130, E131, E139, E140, E141 and E149. In addition, participants were included if they had anatomic therapeutic chemical codes for prescriptions of the anti-diabetic medications A10A and A10B for more than 30 d within the first 3 mo. Patients were excluded if they were prescribed antidepressants (N06A) or anticonvulsants (N03AX12 and N03AX16) within the first 3 mo because these could be used for diabetic neuropathy[14]. Considering the etiology of T2DM, patients older than 30 years of age were included in the study. To exclude other causes of neuropathy, patients with connective tissue diseases (ICD-10 codes: M05, M06, M30, M31, M32, M33, M34, M35 and M45), renal failure (ICD-10 codes: I120, I131, I132, N17, N18 and N19) and malignancy (ICD-10 codes: C00-C97) were excluded at baseline. The first 3 mo were selected as the duration of exposure to statin/metformin/statin + metformin, and exposure to each medication was defined as a prescription for more than 30 d of treatment. Patients who had never been prescribed these medications were defined as the non-exposure group. The statin + metformin non-exposure group was defined as

patients who had not been exposed to statins or metformin. Anatomic therapeutic chemical codes were used to identify prescriptions for statins (C10AA01–C10AA08) and metformin (A10BA02). Patients with combination medications, such as statins with other dyslipidemia or antihypertensive medications or metformin with other anti-diabetic medications, were excluded from the assessment of medication exposure to specifically evaluate the influence of statins or metformin on neuropathy incidence. The incidence of new-onset neuropathy was investigated within the final 9 mo of the index year. The combined disease codes for diabetic neuropathy (ICD-10 codes: E114, E124, E134, E144, G590 and G632) and prescriptions of either tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors or anticonvulsants recommended by the American Diabetes Association[14] [anatomic therapeutic chemical codes: N03AX12 (gabapentin), N03AX16 (pregabalin), N06AA01 (desipramine), N06AA02–N06AA03 (imipramine), N06AA09 (amitriptyline), N06AA10 (nortriptyline), N06AX16 (venlafaxine) and N06AX21 (duloxetine)] for more than 30 d were used to identify patients with new-onset neuropathy. The ICD-10 codes for diabetic neuropathy were selected because the use of anticonvulsants or serotonin-norepinephrine reuptake inhibitors is covered by national health insurance for patients with diabetic neuropathy but not for patients with nonspecific neuropathy. Therefore, in Korea, neuropathy medications (*i.e.* anticonvulsants or antidepressants) are usually prescribed after the submission of the ICD-10 codes for diabetic neuropathy in patients with T2DM. In this study, we identified drug-induced neuropathy by only including patients with ICD-10 codes for diabetic neuropathy and combined prescriptions of antidepressants or anticonvulsants after at least 90 d of exposure to statin/metformin/statin + metformin therapies. The schematic diagram of the research protocol is presented in Figure 1. The patients were divided into the following 10-year age-group intervals: 30–39, 40–49, 50–59, 60–69 and > 70 years.

### Statistical analysis

Baseline demographic characteristics are summarized as numbers and percentages and compared using the  $\chi^2$  test or Fisher's exact test. Propensity score (PS)-matching was performed by 1:1 matching according to age, sex and comorbidities included in the Charlson Comorbidity Index[15]. Logistic regression analyses were performed to calculate crude and PS-matched odds ratios (ORs) for new-onset neuropathy. Values of  $P < 0.05$  were considered to indicate statistical significance. All tests were performed using R software (R for Windows 3.3.2; The R Foundation for Statistical Computing, Vienna, Austria).

## RESULTS

### Comparison of baseline characteristics and incidence of neuropathy between statin/metformin/statin + metformin users and non-users

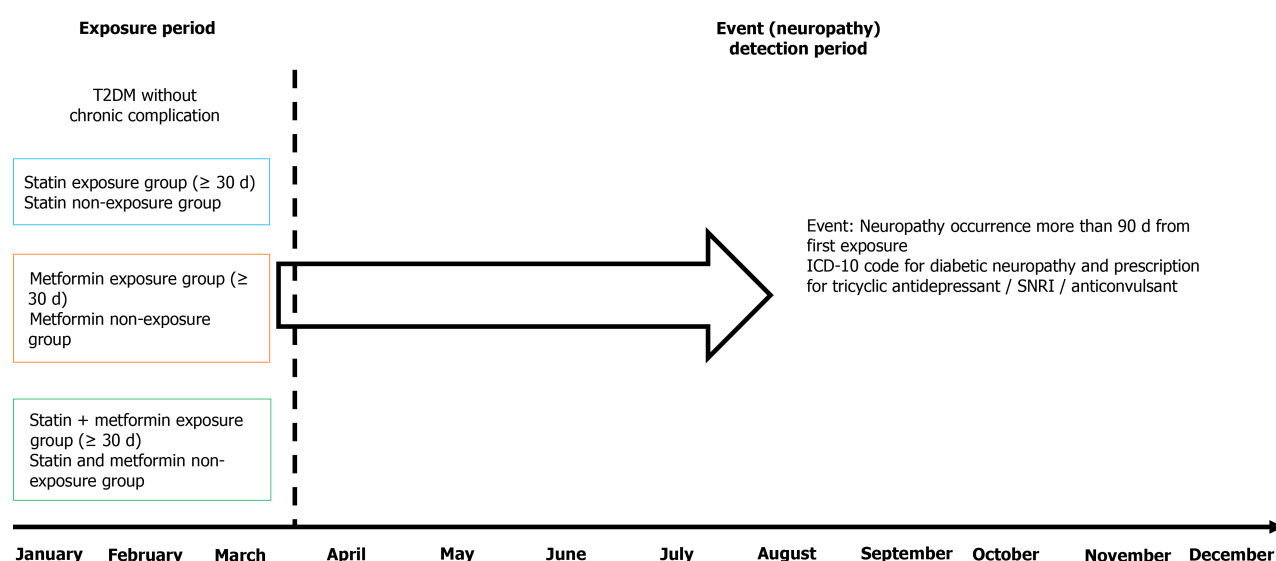
The HIRA-NPS datasets for 2016 and 2017 included 1468033 and 1473083 patients, respectively. In each year, 34964 and 35887 patients had T2DM without diabetic complications, respectively (Figure 2). Statin therapy analyses showed that 17413 patients received statin therapy, and 17267 patients did not receive statin therapy in 2016. In 2017, 18707 patients received statin therapy, and 16882 patients did not. The overall age distributions between the two groups were comparable in both 2016 and 2017 (Supplementary Tables 1 and 2). The incidence of neuropathy was greater in statin users than in statin non-users in 2016 [582/17413 (3.34%) *vs* 477/17267 (2.76%),  $P = 0.0017$ ]. In 2017, statin users had a greater incidence of neuropathy compared with statin non-users, but this difference was not statistically significant [562/18707 (3.00%) *vs* 449/16882 (2.66%),  $P = 0.0507$ ]. However, comparisons after PS matching showed similar results in both 2016 and 2017, such that the incidence of neuropathy was greater in statin users than in statin non-users [2016: 579/17267 (3.35%) *vs* 477/17267 (2.76%),  $P = 0.0014$ ; 2017: 523/16882 (3.10%) *vs* 449/16882 (2.66%),  $P = 0.0160$ ; Table 1].

Metformin therapy analyses showed that 30683 patients received metformin therapy, and 3922 patients did not receive metformin therapy in 2016. In 2017, 31624 patients received metformin therapy, and 4004 patients did not. The overall age distribution did not differ significantly between the two groups in 2016 or 2017 (Supplementary Tables 3 and 4). The incidence of neuropathy was lower in metformin users than in metformin non-users in 2016 [914 (2.98%) *vs* 158 (4.03%),  $P = 0.0004$ ]. In 2017, metformin users had a reduced incidence of neuropathy compared with metformin non-users, but this difference was not statistically significant [959 (3.03%) *vs* 143 (3.57%),  $P = 0.0635$ ]. Comparisons after PS matching showed lower incidences of

**Table 1 Incidence of neuropathy in statin user and non-user group**

	Statin user, <i>n</i> (%)	Statin non-user, <i>n</i> (%)	<i>P</i> value	Propensity score-matched <sup>†</sup>		
				Statin user, <i>n</i> (%)	Statin non-user, <i>n</i> (%)	<i>P</i> value
2016						
Neuropathy incidence	582/17413 (3.34)	477/17267 (2.76)	0.0017	579/17267 (3.35)	477/17267 (2.76)	0.0014
2017						
Neuropathy incidence	562/18707 (3.00)	449/16882 (2.66)	0.0507	523/16882 (3.10)	449/16882 (2.66)	0.0160

<sup>1</sup>Propensity score-matching was performed by including baseline age, gender and comorbidities (myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular accident or transient ischemic attack, dementia, chronic obstructive pulmonary disease, connective tissue disease, peptic ulcer disease, liver disease, hemiplegia, moderate to severe chronic kidney disease, solid tumor, leukemia, lymphoma, AIDS).



**Figure 1 Schematic of the study plan including the medication exposure period and event (newly developed neuropathy) detection period.** Neuropathy was checked as new onset neuropathy that was detected at least 90 d after first exposure to issued medication to reduce detection bias and determine whether new onset neuropathy was affected by these medications. T2DM: Type 2 diabetes mellitus; ICD-10: International Statistical Classification of Diseases and Related Health Problems, 10<sup>th</sup> revision; SNRI: Serotonin-norepinephrine reuptake inhibitor.

neuropathy in metformin users in both 2016 and 2017 (Table 2).

Combined statin + metformin therapy analyses showed that 14524 patients received both therapies in 2016, but 2175 patients received neither therapy. In 2017, 16096 received both therapies, but 2040 patients received neither therapy. The age distributions were comparable between statin + metformin users and non-users in both 2016 and 2017 (Supplementary Tables 5 and 6). In 2016, statin + metformin users had a lower incidence of neuropathy compared with statin + metformin non-users [438 (3.02%) *vs* 83 (3.82%), *P* = 0.0452]. This difference was also present in 2017 but was not statistically significant [472 (2.93%) *vs* 65 (3.19%), *P* = 0.5239]. Comparisons after PS matching showed that the incidences of neuropathy were comparable between the two groups in both 2016 and 2017 (Table 3).

### Risks of neuropathy in statin/metformin/statin + metformin users

Logistic regression analysis demonstrated that statin therapy was significantly and positively associated with neuropathy incidence in both 2016 and 2017 [PS-matched OR = 1.22, 95% confidence interval (CI): 1.08-1.38; PS-matched OR = 1.17, 95%CI: 1.03-1.33, respectively]. Furthermore, metformin therapy was consistently negatively associated with neuropathy incidence in both 2016 and 2017 (PS-matched OR = 0.30, 95%CI: 0.21-0.42; PS-matched OR = 0.44, 95%CI: 0.32-0.60, respectively). Combined statin + metformin therapy was not associated with a significant risk of neuropathy in 2016 or 2017. The results of logistic regression analyses are summarized in Table 4.

**Table 2 Incidence of neuropathy in metformin user and non-user group**

				Propensity score-matched <sup>1</sup>		
	Metformin user, <i>n</i> (%)	Metformin non-user, <i>n</i> (%)	<i>P</i> value	Metformin user, <i>n</i> (%)	Metformin non-user, <i>n</i> (%)	<i>P</i> value
2016						
Neuropathy incidence	914/30683 (2.98)	158/3922 (4.03)	0.0004	49/3922 (1.25)	158/3922 (4.03)	< 0.0001
2017						
Neuropathy incidence	959/31624 (3.03)	143/4004 (3.57)	0.0635	64/4004 (1.60)	143/4004 (3.57)	< 0.0001

<sup>1</sup>Propensity score-matching was performed by including baseline age, gender, and comorbidities (myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular accident or transient ischemic attack, dementia, chronic obstructive pulmonary disease, connective tissue disease, peptic ulcer disease, liver disease, diabetes mellitus, hemiplegia, moderate to severe chronic kidney disease, solid tumor, leukemia, lymphoma, AIDS).

**Table 3 Incidence of neuropathy in statin + metformin user and non-user group**

				Propensity score-matched <sup>†</sup>		
	Statin + metformin user, <i>n</i> (%)	Non-user, <i>n</i> (%)	<i>P</i> value	Statin + metformin user, <i>n</i> (%)	Non-user, <i>n</i> (%)	<i>P</i> value
2016						
Neuropathy incidence	438/14524 (3.02)	83/2175 (3.82)	0.0452	71/2175 (3.26)	83/2175 (3.82)	0.3248
2017						
Neuropathy incidence	472/16096 (2.93)	65/2040 (3.19)	0.5239	62/2040 (3.04)	65/2040 (3.19)	0.7868

<sup>1</sup>Propensity score-matching was performed by including baseline age, gender, and comorbidities (myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular accident or transient ischemic attack, dementia, chronic obstructive pulmonary disease, connective tissue disease, peptic ulcer disease, liver disease, diabetes mellitus, hemiplegia, moderate to severe chronic kidney disease, solid tumor, leukemia, lymphoma, AIDS).

## DISCUSSION

In the present study, we demonstrated an elevated risk of neuropathy among statin users and a reduced risk of neuropathy among metformin users in patients with T2DM. Notably, combined statin + metformin therapy was not associated with new-onset neuropathy in patients with T2DM. These findings were based on real-world insurance claims data from the Korean population. Statins can cause neuropathy, and impaired mitochondrial transport and a reduction in vitamin E levels have been proposed as underlying mechanisms[16]. An analysis of 757 patients with diabetes revealed a significantly greater relative risk of peripheral neuropathy in patients with diabetes who were receiving statin therapy[6]. Our results included a larger sample size than in previous studies and confirmed the elevated risk of neuropathy in patients with T2DM during statin therapy.

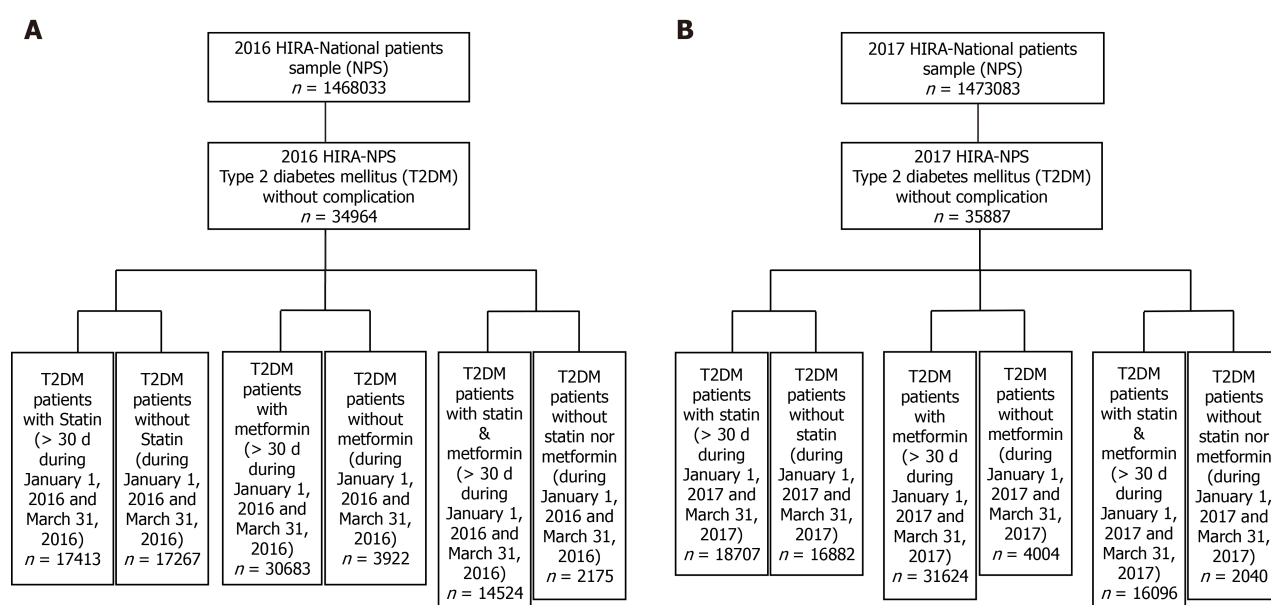
The influence of metformin therapy on neuropathy incidence is not yet established. Strict control of hyperglycemia is the most important treatment principle for preventing diabetic microvascular complications including neuropathy[17], and metformin exerts anti-diabetic effects *via* several mechanisms. Therefore, metformin can function to prevent the onset of diabetic neuropathy. In an animal study, metformin treatment protected against neural damage by increasing the levels of neural growth factor, vascular endothelial growth factor and anti-inflammatory factors [18]. Another animal study demonstrated that metformin preserved peripheral nerve fiber density and that the beneficial effects of metformin were comparable with those of alpha lipoic acid, an antioxidant used in the clinical treatment of diabetic neuropathy[19].

By contrast, metformin causes vitamin B12 deficiency and may subsequently induce diabetic neuropathy[20]. In a cross-sectional study, low to borderline vitamin B12 levels were more common in patients with diabetic neuropathy than in patients without (64% *vs* 17%)[9]. However, another study demonstrated a non-significant

**Table 4 Logistic regression analyses for neuropathy occurrence in 2016 and 2017 Health Insurance Review and Assessment national patient sample data**

			Propensity score-matched <sup>1</sup>	
	OR	95%CI	OR	95%CI
2016				
Statin use	1.22	1.07-1.38	1.22	1.08-1.38
Metformin use	0.73	0.61-0.87	0.30	0.21-0.42
Statin + metformin use	0.78	0.62-1.01	0.85	0.61-1.19
2017				
Statin use	1.13	1.00-1.29	1.17	1.03-1.33
Metformin use	0.84	0.71-1.02	0.44	0.32-0.60
Statin + metformin use	0.92	0.70-1.21	0.95	0.66-1.38

<sup>1</sup>Propensity score-matching was performed by including baseline age, gender, and comorbidities (myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular accident or transient ischemic attack, dementia, chronic obstructive pulmonary disease, connective tissue disease, peptic ulcer disease, liver disease, diabetes mellitus, hemiplegia, moderate to severe chronic kidney disease, solid tumor, leukemia, lymphoma, AIDS). OR: Odds ratio; CI: Confidence interval.



**Figure 2 Flow charts of the step-wise inclusion of participants from the 2016 and 2017 Health Insurance Review and Assessment national patient sample. A: 2016; B: 2017. HIRA: Health Insurance Review and Assessment; NPS: National patient sample; T2DM: Type 2 diabetes mellitus.**

association between metformin therapy and vitamin B12 levels and showed that vitamin B12 levels were not associated with the severity or prevalence of neuropathy in patients with T2DM[10]. The vitamin B12 reductions were dose-dependent in patients with T2DM who were receiving metformin therapy, and patients with metformin daily doses greater than 1500 mg had a significant risk of vitamin B12 deficiency[21]. In the present study, we found a reduced risk of neuropathy in patients with T2DM who were receiving metformin therapy. Further studies to stratify patients according to metformin daily doses and prospectively collect vitamin B12 and blood glucose levels could reveal whether metformin dose influences the incidence of neuropathy and which aspect (vitamin B12 or blood glucose) more strongly influences neuropathy development during metformin therapy.

We demonstrated that combined metformin + statin therapy did not enhance or reduce the risk of neuropathy in patients with T2DM, although statin therapy enhanced the risk of neuropathy and metformin therapy reduced the risk of neuropathy in these patients. The present results do not clearly indicate whether



concomitant metformin administration can reduce the risk of statin-induced neuropathy in patients with T2DM because the findings were based on epidemiological data. However, metformin is regarded as background anti-diabetic medication and is used in most patients with T2DM, except those with contraindications or severe metformin-related side effects[4,8]. Our results suggest a beneficial effect of metformin in terms of reducing the risk of neuropathy, especially in patients with T2DM who are receiving statin therapy.

There were some limitations in the present study. First, the data were retrospectively collected and did not include important baseline characteristics (*e.g.*, duration of T2DM and doses of each medication). Although PS matching was used to reduce the effects of confounders, unidentified confounders or selection biases might have been present. Therefore, the enhanced neuropathy risk associated with statin therapy does not directly indicate a role for statins in the onset of neuropathy. Similarly, the reduced neuropathy risk associated with metformin therapy does not directly indicate a protective role of metformin against the onset of neuropathy. Second, claims data have intrinsic limitations in terms of possible misdiagnosis and misprescription, and it is difficult to distinguish between T2DM-induced and medication-induced neuropathies. However, HIRA-NPS data are extracted from the overall Korean population and are therefore suitable for the assessment of specific disease risks. Third, HIRA-NPS data only provide 1-year follow-up data for each index year, which is a relatively short time period. Fourth, although the NPS sample was collected using a stratification strategy and could be analyzed easily, it only included approximately 3% of the overall health insurance claims data. Therefore, the analysis of data collected over longer time periods from larger samples should be performed in future studies. Furthermore, *in vivo* and *in vitro* basic research is needed to determine the mechanisms by which statins and metformin contribute to the onset or prevention of neuropathy.

## CONCLUSION

We demonstrated the influence of statin and metformin therapies on the incidence of neuropathy in patients with T2DM. Statin therapy enhanced the risk of neuropathy in patients with T2DM, whereas metformin therapy reduced this risk. Combined statin + metformin therapy did not have a significant impact on the incidence of neuropathy. Therefore, when prescribing statin therapy for patients with T2DM, physicians should assess the potential for neuropathy development and consider the addition of metformin to reduce this risk.

## ARTICLE HIGHLIGHTS

### Research background

Statin and metformin are widely used medications in patients with type 2 diabetes mellitus (T2DM). These medications have been claimed as causative agents for neuropathy.

### Research motivation

To identify the incidence and risk of statin, metformin and statin + metformin therapy on new onset neuropathy.

### Research objectives

The incidence of neuropathy was evaluated and compared between T2DM patients who used or did not use statin/metformin/statin + metformin by using Korean Health Insurance Review and Assessment - national patient sample data.

### Research methods

The prospective cohort study used nation-wide health insurance data.

### Research results

Statin therapy showed a positive association (odds ratio = 1.22, 95% confidence interval: 1.08-1.38], whereas metformin therapy showed a negative association with new onset neuropathy (odds ratio = 0.30, 95% confidence interval: 0.21-0.42) in

patients with T2DM. Combination therapy of statin and metformin did not have an effect on new onset neuropathy of T2DM patients.

### Research conclusions

The widely used medications in T2DM, statin and metformin, could have an effect on neuropathy development in T2DM patients. Physicians should pay attention to new onset neuropathy when using statin in T2DM patients.

### Research perspectives

Nevertheless, further studies are required to reveal underlying mechanisms of statin and metformin on new onset neuropathy of T2DM.

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