Scientific Reports

https://doi.org/10.1038/s41598-026-42229-0

Article in Press

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Received: 16 December 2025

Accepted: 25 February 2026

Published online: 01 March 2026

Cite this article as: Xu M., Gao X., Liu Z. *et al.* The effect of medication use on chronic pruritus in patients with type 2 diabetes mellitus: a multicenter cross-sectional study. *Sci Rep* (2026). https://doi.org/10.1038/s41598-026-42229-0

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The effect of medication use on chronic pruritus in patients with type 2 diabetes mellitus: A multicenter cross-sectional study

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Abstract

Background : This study aimed to investigate the association between various types of medications and chronic pruritus (CP) in patients with type 2 diabetes mellitus (T2DM) through a large cross-sectional study.

Methods: This study encompassed data from the Tianjin Community-Based Diabetic Retinopathy Screening Cohort, comprising 2,059 patients with T2DM who were enrolled from eight community centers. The exposure variables were different medication classes, and the outcome variable was CP symptoms.

Results: The prevalence of CP in patients with T2DM was 41.3% (851/2059). After adjusting for potential confounding factors, α-glucosidase inhibitor (AGIs) (adjusted OR 1.272, 95%CI 1.050 - 1.541), DPP-4 inhibitors (DPP-4is) (adjusted OR 1.286, 95%CI 1.006 - 1.642), and statins(adjusted OR 1.411, 95%CI 1.151 - 1.729) remained independently associated with higher odds of CP. In addition, the odds of CP increased progressively with the number of medications used (from one to three drugs; ORs ranging from 1.230 to 1.961). Subgroup analyses further identified a significant interaction between AGI use and renal impairment, with higher odds of CP observed among patients with renal impairment. (P for interaction < 0.05)

Conclusion: CP in patients with T2DM was associated with the use of AGIs, DPP-4is, and statins. Moreover, a significant interaction was observed between

renal impairment and the use of AGIs.

Keywords: Type 2 diabetes mellitus; Chronic pruritus; Antidiabetic agents; Statins; Multicenter study

Introduction

Type 2 diabetes mellitus (T2DM) has become a serious public concern , with the burden of disease continuing to grow and projected to increase b y 25% by 2030 and 51% by 2045 [1,2]. In addition to its well-recognized m acrovascular and microvascular complications, T2DM is frequently accompa nied by dermatologic manifestations, among which chronic pruritus (CP) is common yet often underrecognized [3]. Epidemiologic studies have shown t hat the prevalence of CP in diabetic patients is significantly higher than th at in the general population, with approximately 30–40% of patients afflicte d with varying severity of CP [4]. The harm caused by CP should not be ig nored, and previous studies have revealed that CP is significantly associate d with depression and suicidal ideation and also can cause sleep disorders, mood disorders, and negative psychosocial impacts—ultimately leading to a significant decline in one's quality of life[5].

Patients with T2DM frequently manifest multiple metabolic disorders su ch as hypertension and dyslipidemia [6-8]. In clinical practice, multiple med ications are often required for combination therapy to achieve sustained co ntrol of blood glucose, blood pressure[9–11]. However, although combinatio n therapy is effective in reducing the risk of cardiovascular complications, i t also generates challenges such as an elevated risk of drug–drug interacti ons, an increased burden on the liver and kidneys, and reduced patient co

mpliance. At present, relevant research has shown that CP in patients with T2DM may be associated with multiple underlying pathologic mechanisms of diabetes, including nerve damage caused by abnormal glucose metabolis m, skin barrier dysfunction, and chronic inflammatory reactions [12, 13]. In addition, many studies have confirmed that certain antidiabetic agents, ant ihypertensive agents, antihyperlipidemic agents, and antiplatelet agents are also associated with adverse skin reactions [14-17]. These studies suggest that the problem of potential drug-induced pruritus cannot be ignored.

Despite this, there is currently a paucity of research on the independen t or synergistic effects of multiple-drug regimens on pruritus symptoms in patients with T2DM. In-depth exploration of these issues is therefore of gre at clinical value for optimizing the management of comorbidities and impro ving the quality of life of patients. This would be particularly useful for pat ients who need to control multiple metabolic indicators simultaneously to e nsure that the indicators meet the standards while minimizing the odds of skin complications.

This study was based on a population cohort from multiple primary car e communities in Tianjin, and we herein investigated the cross-sectional as sociation between the adoption of different classes of antidiabetic agents, a ntihypertensive agents, antihyperlipidemic agents, and antiplatelet agents a nd CP in patients with T2DM. Our findings aim to provide epidemiologic e

vidence to inform the optimization of combination therapy in patients with T2DM while considering dermatologic.

Methods

Study design and population

All data in this study were derived from the Tianjin Diabetic Retinopathy Screening Cohort, which surveyed 3,024 patients with T2DM who participated in the Tianjin Diabetic Retinopathy Community Screening Program at eight different community centers between April and August of 2024. Prior to the formal survey, patients with primary dermatologic diseases were excluded, during screening, participants were systematically asked whether they had a past or current history of primary skin disorders, such as eczema, psoriasis, neurodermatitis, or allergic dermatitis, and whether they were currently using antipruritic medications or treatments for primary skin conditions. Our inclusion criteria were (1) pruritus lasting ≥6 weeks; (2) a diagnosis of T2DM of ≥3 months; (3) a patient age of 20–90 years. The exclusion criteria were (1) patients who were unable to complete the study or had missing pruritus data; (2) patients with tissue damage, malignant tumors, or acute infection, thyroid disease; (3) alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels >2.5 times the upper limit, with total bilirubin (TIBL) >normal upper limit; and (4) an estimated glomerular filtration rate (eGFR) <45 mL/min/1.73 m2. Type 2 diabetes patients who met the abovementioned inclusion and exclusion

criteria were then included in this study according to the flow chart shown in Figure 1.

This study was conducted in accordance with the Declaration of Helsinki (1964), as revised in 2008, and was approved by the Ethics Committee of Tianjin Medical University Eye Hospital. We conducted a cross-sectional study, and all participants provided written informed consent. This study was conducted in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for cross-sectional studies.

Potential covariates

CP was assessed using a questionnaire-based survey. Participants were asked to recall their average level of pruritus over the previous 3 months. Pruritus severity was quantified using the Numerical Rating Scale (NRS), ranging from 0 (no pruritus) to 10 (worst pruritus). An NRS score ≥3 was defined as the presence of clinically relevant CP and used as the outcome criterion. Demographic information such as patient age, sex (male, female), duration of diabetes, smoking status (never, former, or current), antihypertensive agents (no, yes), antihyperlipidemic agents (no, yes), antidiabetic agents (no, yes), antiplatelet agents (no, yes), and types of antidiabetic agents, antihyperlipidemic agents, antihypertensive agents, and antiplatelet agents used were also collected. Medication use was assessed for the 3 months preceding the survey. If a medication change occurred within the 3-month

window, exposure was classified according to the medication category used for the longest duration. We collected fasting venous blood from patients and measured their triglyceride (TG,mmol/L), low-density lipoprotein (LDL-C, mmol/L), high-density lipoprotein (HDL-C, mmol/L), glycated hemoglobin (HbA1c, %), fasting blood glucose (FBG, mmol/L), ALT (U/L), AST (U/L), estimated glomerular filtration rate (eGFR, mL/min/1.73m^2), serum creatinine (μmol/L), and urine albumin-to-creatinine ratio (UACR, mg/g). All tests were performed by the NHC Key Laboratory of Hormones and Development, Chu Hsien-I Memorial Hospital, and Tianjin Institute of Endocrinology, using fully automated biochemical analyzers. The formula we used for estimating eGFR) was the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [18].Data integrity was high across all variables included in the regression models, with most indicators showing no missing values. Given that the overall missing rate was negligible and did not involve primary exposure or outcome variables, its impact on the statistical power is considered limited.

Statistical analysis

We conducted statistical analysis using R (version 4.4.1), described bas eline characteristics, and expressed quantitative data that followed a norma l distribution as mean±SD; group comparisons were then executed using St udent's *t* test. Categorical variables from non-normal distributions were exp ressed as median and interquartile range, and groups compared using the

Mann–Whitney U or Chi-squared test. Univariate logistic regression was initially performed to evaluate the crude associations between medication use and diabetic pruritus. Covariates for the multivariable models were selected based on an integration of univariate results and a priori clinical considerations. Notably, parameters including eGFR, FBG, HbA1c, liver enzymes (ALT, AST), TBIL, and lipid profiles (TG, LDL-C) were force-entered into the final adjusted model (Model 3). Although these variables did not reach statistical significance in univariate analyses or trigger a >10 change in the effect estimates of primary exposures, they were retained to ensure the biological plausibility of the model, given their established relevance to systemic metabolic status and the pathophysiology of chronic pruritus. Multicollinearity was rigorously assessed using variance inflation factors (VIFs), and all variables in the final model exhibited VIF values <3, indicating no significant collinearity.[19]. Model 1 represented unadjusted data; Model 2 was adjusted for age, sex, BMI, smoking status, diabetes duration, use of antihypertensive drugs, and antiplatelet drugs; and Model 3 was adjusted for eGFR, PBG, HbA1c, ALT, AST, UACR, TG, LDL-C, and TBIL in addition to the variables in Model 2 ($P < 0.05$ was considered statistically significant).

To further investigate the potential cumulative associations of concurrent therapies with CP risk, we conducted a pre-planned exploratory analysis focusing on the combined use of AGIs, DPP-4is, and statins. These agents

were selected based on their prevalence in clinical practice and their initial associations observed in our primary models. Participants were categorized into four mutually exclusive groups according to their medication burden regarding these three classes: none (reference group), any one, any two, or all three. Multivariable logistic regression (Models 1–3) was then employed to assess the trend of CP risk across these exposure clusters.

Finally, by incorporating stratified analysis and interaction tests into the regression model, we assessed the potential moderating effects of sex (male, female), age groups (<60 years, ≥60 years), diabetes-duration groups (<10 years,≥10 years), eGFR groups (<60 mL/min/1.73 m2,≥60 mL/min/1.73 m2), and smoking status (never smoked, smoker, quit smoking) on the symptoms of CP in patients with diabetes.

Results

A total of 2,059 patients with T2DM comprised this study, with 851 (41.3%) reporting CP symptoms and 1,208 (58.7%) not reporting symptoms of CP (Table 1 shows the comparison of baseline demographic and clinical characteristics according to CP symptoms, divided into a non-pruritus group [n=1208] and a pruritus group [n=851]) based on the presence or absence of CP symptoms. There were no significant statistical differences between the two groups in

terms of sex composition, mean age, glycated hemoglobin (HbA1c), fasting blood glucose (FBG) concentrations, liver function indicators (ALT and AST), bilirubin levels, kidney function indicators (eGFR, UACR), and lipid parameters (TC, TGs, LDL-C, and HDL-C) (all $P > 0.05$). However, intergroup comparisons revealed that patients in the pruritus group exhibited the following characteristics: a significantly longer duration of diabetes ($P < 0.001$), greater use of antidiabetic agents ($P=0.045$), and more widespread use of lipid-lowering medications ($P=0.002$).

We performed additional Chi-squared tests on the relationship between different types of antidiabetic agents/antihyperlipidemic agents and CP symptoms and ascertained that the proportions of individuals using AGIs, dipeptidyl dipeptidase inhibitors (DPP-4is), and insulin injections in the pruritus group were significantly higher than those in the non-pruritus group ($P=0.004$, $P=0.031$, $P=0.011$ respectively). Among antihyperlipidemic agents, the use of statins was higher in the pruritus group than in the non-pruritus group (46.2% vs. 39.2%), respectively ($P<0.01$; Supplemental table 1 and 2).

To more accurately assess the effect strength of each factor, we further conducted a single-factor regression analysis on variables with statistical significance, and results are shown in Table 2. The applications of AGIs (OR = 1.293; 95% CI, 1.071–1.692), DPP-4is (OR = 1.305; 95% CI, 1.071–1.692), and insulin injections (OR = 1.305; 95% CI, 1.022–1.543) were significantly

positively associated with CP symptoms (P values of 0.004, 0.011, and 0.031, respectively, with ORs >1). The administration of statins also demonstrated a significant association (OR = 1.302; 95% CI, 1.117–1.592; P = 0.001) and was similarly positively correlated (OR >1).

Based on our single-factor analysis, we then executed a multiple regression model to adjust for potential confounding factors (including demographic characteristics, clinical indicators, and medication use; the results of this analysis are shown in Table 3). While the use of AGIs, DPP-4is, and statins remained significantly associated with CP symptoms (all P < 0.05), the use of insulin injections lost statistical significance after adjusting for confounding factors (P > 0.05), this suggests that the observed association between insulin use and CP was more likely attributable to diabetes severity and progression than to an independent effect.

Subsequently, we conducted an exploratory combined exposure analysis focusing on the three medication classes that retained statistical significan ce in the multivariable models: AGIs, DPP-4is, and statins. As shown in Tab le 4, compared with the non-use group, the likelihood of experiencing CP s ymptoms demonstrated a progressive upward trend as the number of concu rrent medications increased.In the fully adjusted model (Model 3), single-dr ug use was associated with a higher likelihood of CP, although it did not r each independent statistical significance (OR = 1.243, 95% CI: 0.972–1.596)

. However, the dual-drug use group exhibited a significantly higher prevale nce of CP symptoms (OR = 1.788, 95% CI: 1.353–2.368, P < 0.001). The tr iple-drug use group showed the highest association with CP, with an OR of 2.113 (95% CI: 1.308–3.426, P < 0.01). This cumulative trend remained ro bust across all three models, suggesting a positive dose-response-like relati onship between the medication burden and the odds of CP.To further delin eate the nature of these associations, we evaluated the second- and third-o rder interactions among these agents. Our results showed no statistically si gnificant evidence of interaction (P > 0.05, Supplemental table 3). While t his pattern is consistent with additive actions of the medications on CP pre valence within this cohort, we cautiously interpret this as a lack of evidenc e for significant departure from additivity, rather than definitive proof of th e absence of synergistic mechanisms.

Subgroup analyses and interaction tests (Table 5) revealed that the ass ociations between medication use and CP were generally consistent across most clinical strata. Notably, a significant interaction was observed between AGI use and renal function (P for interaction = 0.024), where the likelihoo d of reporting CP was markedly higher in patients with eGFR in 45-60 mL/ min/1.73 m^2 (OR = 6.4, 95% CI: 2.03–24.36) compared to those with prese rved renal function. This exploratory finding suggests that impaired renal c learance might potentiate the pruritic effects of AGIs. No other significant i

nteractions were detected across the studied subgroups, indicating that the ir associations with CP remain relatively stable regardless of age, sex, or d iabetes duration.

Discussion

This cross-sectional study demonstrated that the use of AGIs, DPP-4 inhibitors, and statins was significantly associated with CP symptoms in patients with T2DM. Subsequent analyses suggested a potential interaction between AGI use and CP symptoms among patients with renal impairment.

In the present study, 41.3% of patients with T2DM reported CP symptoms, a proportion higher than that observed in the general population in previous reports [20–22].Although no significant differences in HbA1c or fasting blood glucose levels were observed at baseline between patients with and without CP, the absence of a cross-sectional association does not exclude a contribution from long-term metabolic dysregulation. The pruritic effects of hyperglycemia may reflect cumulative metabolic stress rather than contemporaneous glucose measurements. Chronic hyperglycemia can lead to persistent skin dehydration, reduced glandular secretion [23], and diabetic peripheral neuropathy, including sensory nerve dysfunction and aberrant neural firing [24], which may further contribute to the development of CP.

With the increasing implementation of multiple pharmacologic agents in

T2DM management, adverse drug reactions have also garnered growing concern. Some previous studies have clarified the adverse skin reactions of certain antidiabetic and antihyperlipidemic agents, but there has been a paucity of large-sample systematic studies on patients with T2DM. Based on these studies, we therefore innovatively analyzed the correlation of various types of antidiabetic and antihyperlipidemic agents with CP symptoms in patients with T2DM and adjusted multiple confounding factors that may lead to CP to make up for the shortcomings of previous investigations. In our study, we ascertained that AGIs, DPP-4is, and statins were independently associated with CP after adjusting for confounding factors. Our findings are supported by some theoretical evidence: Kowalska et al., e.g., reviewed the literature and case reports on adverse skin reactions to various oral antidiabetic agents and found that patients using AGIs experienced adverse skin complications such as rash, CP, and hyperhidrosis. Case reports have also shown that acarbose induced systemic erythema multiforme [25]. In terms of the mechanisms underlying the association between CP and DPP-4is, several studies have demonstrated a significant association between DPP-4is and a type of immune disease known as bullous pemphigoid [26]. The average concentrations of IL-5, CCL1, CCL17, and CCL26 in the skin of patients with DPP4i-BP were shown to be higher than those in normal BP [27], and these cytokines are related to the chemotaxis of eosinophils, which may also comprise a hypothesis for its association with

chronic pruritus symptoms in patients with T2DM. Statins lower cholesterol synthesis by inhibiting HMG-CoA reductase, thereby reducing the synthesis of mevalonic acid derivatives [28]; this may also directly act on T cells to alter the balance between Th1 and Th2 [29-30]. Changes in the Th1/Th2 balance can disrupt immune homeostasis, facilitating the production of IgE-mediated CP responses by B cells. The adverse skin reactions associated with statins have also been confirmed in multiple clinical studies [31].However, these associations should be interpreted with caution because of potential confounding by indication. DPP-4 inhibitors, insulin, and statins are more commonly used in some patients with complications, and these factors themselves may be associated with CP, which is also a limitation of this article.

In scenarios that involve multiple drug treatments and long-term medication, the cumulative risks of drug interactions and side effects are clinical issues that cannot be ignored. In this study, we further analyzed the effects of multiple drug combinations on CP in patients with T2DM and demonstrated that there was an increase in risk when statins, DPP-4i, and AGIs were used in combination. The potential mechanism underlying this increased odd may be related to the metabolic pathways associated with the medications. A majority of statins [32] and some DPP-4 inhibitors [33] are primarily metabolized by the CYP3A4 enzyme, and when applied in combination, these medications may compete for binding sites on CYP3A4, leading to an additive risk of adverse effects. Statins

may elevate hepatic transaminase levels [34], and although DPP-4is and AGIs manifest low hepatotoxicity when used alone, triple therapy may enhance the risk of liver damage due to an increased metabolic burden. In addition, AGIs are excreted by the kidneys, and when used in combination with statins that are also excreted by the kidneys, patients with renal impairment may be at an increased risk of kidney damage due to drug accumulation.

Finally, this study revealed that AGI users with renal impairment (i.e., an eGFR 45-60) possessed a significantly increased risk of CP, which has been related to the pharmacokinetics of the medication. Pharmacokinetic studies of AGIs have shown that 1–2% of oral AGIs are absorbed in the gastrointestinal tract, and almost all of the remainder is excreted in the urine [35]. This promotes drug accumulation in patients with renal impairment, and the accumulated AGIs and their metabolites may act on skin nerve endings or modulate the skin microenvironment; this may further explain why AGI users with renal impairment (eGFR <60) demonstrate a significantly increased risk of CP. We excluded participants with an eGFR <45 and severe liver dysfunction to minimize confounding by advanced systemic disease, which is a clearly independent cause of chronic pruritus. It is possible that uremic or cholestatic pruritus may predominate in patients with moderate-to-severe renal or hepatic impairment, and the mechanisms associated with diabetes are unknown. We cannot rule out a potential effect of liver and renal function on pruritus, but this

could have contributed to the reduced prevalence of the data.

Given the current dearth of large-scale clinical data and the absence of a unified research framework for the synergistic analysis of various medications, we explored the association between different medications used alone or in combination with CP in patients with diabetes. During our analysis, we adjusted for several potential factors that may cause pruritus, including indicators directly or indirectly related to CP such as renal function, liver function, and bilirubin, and explored the risk factors for CP symptoms in patients with diabetes from multiple dimensions. This study thus provides additional evidence based on real-world data for future research; identifies the independent association of statins, AGIs, and DPP-4 inhibitors with chronic pruritus; and can be used to predict the potential additive risk effects of drug combinations. Our investigation creates a foundation for optimizing statin treatment regimens in clinical practice with patients showing CP and enables the prediction of possible additive risk effects of drug combinations. We recommend that physicians give greater attention to the potential adverse skin reactions of medications when selecting hypoglycemic and lipid-lowering drugs, particularly for high-risk populations such as individuals with renal impairment to achieve more accurate individualized treatment plans. DPP-4is, AGIs, and statins are commonly used medications for the treatment of diabetes, and their application is associated with CP in patients with T2DM. Although this relationship is currently

unelucidated, a greater understanding of the effects of such drugs on the immune system, liver and kidney function, skin barrier, and intestinal microbiota may provide a biological basis for the occurrence of CP symptoms.

There were several limitations to the present study. First, our study design was cross-sectional, and although confounding factors were adjusted in our multiple regression analysis, the inherent characteristics of observational studies precluded the establishment of a causal relationship of DPP-4is, AGIs, and statins with pruritus symptoms in patients with diabetes. Future studies should incorporate multicenter, large-sample prospective cohort studies to further validate a potential longitudinal association. Second, although we performed subclass analyses for major drug categories, we lacked detailed data regarding specific medication dosages and the exact duration of therapy. The absence of a dose-response or time-response analysis limits our ability to further characterize the pharmacological impact of these agents on pruritus risk. Future prospective studies should incorporate precise longitudinal data on medication dose and duration, as well as subclass analyses based on metabolic pathways and target differences, to provide more granular evidence for clinical precision medicine.Third, although the pathophysiological mechanisms underlying pruritus involve neuroimmune regulation and receptor signaling, we did not include key biomarkers such as inflammatory factors (e.g., IL-6, IL-2) and κ-opioid receptor distribution; we may therefore have overlooked potential

confounding pathways, and due to the retrospective nature of data collection, certain potentially relevant factors—such as blood pressure control, the skin dryness, and thyroid function. The absence of these variables may introduce residual confounding. Future studies incorporating a more comprehensive range of dermatological and systemic indicators are required to refine these associations. Fourth, sample-size limitations may have resulted in insufficient statistical power for appropriate subgroup analyses. Finally, CP symptom data were collected through interviews, and while standardized questionnaires were adopted, participants' subjective descriptions of symptoms may have been influenced by their cultural background, cognitive level, and recall bias. We recommend that investigators combine objective biomarkers in the future to improve assessment accuracy.

Conclusion

This study systematically revealed for the first-time ever an independent association of AGIs, DPP-4is, and statins with CP in patients with T2DM and uncovered a possible additive odds of drug combination therapy. These findings suggest that clinical monitoring of CP symptoms may be warranted for T2DM patients receiving AGIs, DPP-4is, or statins, particularly when these agents are used in combination. Our results encourage clinicians to review medication profiles and maintain vigilance regarding potential cutaneous side effects in individualized therapeutic strategies. Future large-scale cohort studies and

investigations into the underlying molecular mechanisms of drug-drug interactions are essential to provide more comprehensive evidence and optimize treatment options for patients with T2DM.

Funding

This study was supported by National Natural Science Foundation of China [grant number 82570950], the China Endocrine Metabolism Talent Research Fund [grant number 2023-N-03-15], Bethune Charitable Foundation [grant number Z04JKM2022E035], Science and Technology Fund of Tianjin Municipal Education Commission (2024ZD036, 2023KJ103), Key Project of Science and Technology Fund of Tianjin Municipal Health Commission (TJWJ2025ZD004), and the Tianjin Key Medical Discipline (Specialty) Construction Project [grant number TJYXZDXK-032A],Tianjin Key Medical Discipline Construction Project [grant numberTJYXZDXK-3-007B].

Ethics statement

All data in this study were derived from the Tianjin Diabetic Retinopathy Screening Cohort. The study was approved by the Ethics Committee of Tianjin Medical University Eye Hospital (Ethics Number: 2024KY-10), and written informed consent was obtained from all participants.

Data availability statement

The data that support the findings of this study are available from the

corresponding author upon reasonable request.

Conflicts of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Contributions

MinXu, Ximan Gao,Juping Liu and Saijun Zhou were responsible for the conceptualization of the study; Ximan Gao and Zirong Liu analyzed the statistics; MinXu, Ximan Gao,Zirong Liu,Li Zhang, Zhanglong Wang,Huiru Zhuang, Wenlong Fu, Siyu Yao and Lin zhang collected data; Ximan Gao prepared figures and tables; MinXu and Ximan Gao wrote the original manuscript; Juping Liu and Saijun Zhou reviewed and edited the manuscript. All authors contributed to the article and approved the submitted version

Acknowledgments

The authors would like to express their gratitude to all the patients and staff who participated in the study, all the participants contributed to this research and supported the publication of the article.

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Table 1. Baseline characteristics of patients based on the presence or absence of pruritus.

Variable	Pruritus status		P value
	No Pruritus	Pruritus	
Participants	1208(58.7%)	851(41.3%)	
Males,N (%)	496 (41.1%)	373 (43.8%)	0.201
Age,year	69（65, 73）	69（65, 73）	0.699
BMI,kg/m²	24.78 (22.66-27.18)	24.67 (22.51-26.84)	0.125
Diabetes Duration,year	10（5, 16）	10（6, 20）	<0.001**
Smoking status			0.563
Never smoked,N(%)	949 (78.6%)	639 (75.1%)	
Current smoker,N(%)	198 (16.4%)	143 (16.8%)	
Former smoker,N(%)	61 (5.0%)	69 (8.1%)	
HbA1c,%	6.7 (6.2 ,7.5)	6.8 (6.3, 7.5)	0.637
FBG,mmol/L	7.51 (6.47,8.79)	7.54（6.50, 8.79）	0.804
ALT,U/L	18.60（14.00, 24.76）	18.72（14.00, 25.60）	0.780
AST,U/L	17.71（15.00, 21.13）	18.00（15.20, 21.50）	0.385
eGFR,mL/min/1.73m²	91.52（79.45, 97.71）	93.05（79.46, 98.31	0.183
UACR(mg/g)	9.42（4.12, 25.00）	9.42（4.12, 25.00）	0.273
TG,mmol/L	1.47（1.07, 2.04）	1.43（1.03, 2.05）	0.614
LDL-C,mmol/L	3.05（2.34, 3.72）	2.99（2.30, 3.66）	0.329
HDL-C,mmol/L	1.29（1.12, 1.53）	1.30（1.13, 1.56）	0.501

TBIL,mmol/L	11.80（9.60, 14.19）	11.78（9.33, 14.00）	0.261
Antiplatelet Drugs,N(%)	361 (29.9%)	268 (31.5%)	0.209
Antihypertensive Drugs,N(%)	755 (62.5%)	537 (63.1%)	0.276
Antidiabetic Drugs,N(%)	1097 (90.8%)	793 (93.2%)	0.045*
AntihyperlipidemicDrugs ,N(%)	530 (43.9%)	431 (50.6%)	0.002**

*P < 0.05，**P < 0.01，***P < 0.001

Values are presented as median (interquartile range) or number (%).

HbA1c, glycated hemoglobin A1c; FBG, fasting blood glucose; ALT, alanine aminotransferase; AST, aspartate aminotransferase; eGFR, estimated glomerular filtration rate; UACR, urine albumin-creatinine ratio; TG, triglycerides; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol ;TBIL,total bilirubin.

Table 2. Univariate logistic regression analysis

Variable	Pruritus Status		Pruritus OR (95%CI)	P value
	No Pruritus	Pruritus		
AGIs,N (%)	623 (51.6%)	493 (57.9%)	1.293 (1.084 - 1.543)	0.004*
DPP-4is,N (%)	189 (15.6%)	170 (20.0%)	1.346 (1.071 - 1.692)	0.011*
Injectable Insulins,N (%)	260 (21.5%)	218 (25.6%)	1.256 (1.022 - 1.543)	0.031*
Statins,N (%)	473 (39.2%)	393 (46.2%)	1.333 (1.117 - 1.592)	0.001*

*P < 0.05, **P < 0.01, ***P < 0.001

Table 3. Multivariate logistic regression analysis

	Pruritus OR (95%CI)		
	Model 1	**Model 2**	**Model 3**
Variable			
AGIs	1.265 (1.057 - 1.513)**	1.263 (1.047 - 1.523)*	1.272 (1.050 - 1.541)*
DPP-4is	1.343 (1.066 - 1.691)*	1.342 (1.058 - 1.703)*	1.286 (1.006 - 1.642)*
Injectable Insulins	1.196 (0.969 - 1.474)	1.085 (0.859 - 1.369)	1.032 (0.810 - 1.314)
Statins	1.343 (1.066 - 1.691)**	1.085 (0.859 - 1.369)**	1.411 (1.151 - 1.729)**

*P < 0.05, **P < 0.01, ***P < 0.001

Model 1 was adjusted for none; Model 2 was adjusted for age, sex, BMI, smoking status, diabetes duration, Antihypertensive Drugs, Antiplatelet Drugs; Model 3 was adjusted for age, sex, smoking status, diabetes duration, Antihypertensive Drugs, Antiplatelet Drugs, eGFR, FBG, HbA1c, ALT, AST, TBIL, TG, LDL-C.

Table 4. Multivariate logistic regression analysis of drug combinations

	Pruritus OR (95%CI)		
	Model 1	**Model 2**	**Model 3**
Variable			
Non-use[a]	REF	REF	REF
Single-drug use[b]	1.267 (1.007 - 1.598)*	1.264 (0.993 - 1.614)	1.243 (0.972 - 1.596)
Dual-drug use[c]	1.744 (1.356 - 2.247)***	1.793 (1.365 - 2.361) ***	1.788 (1.353 - 2.368) ***
Triple-drug use[d]	1.961 (1.314 - 2.930)**	2.178 (1.371 - 3.472)**	2.113 (1.308 - 3.426)**

*P < 0.05, **P < 0.01, ***P < 0.001

[a]No DPP-4is and AGIs and Statins; [b]DPP-4is or AGIs or Statins; [c]DPP-4is and AGIs or DPP-4is and Statins or AGIs and Statins; [d]DPP-4is and AGIs and Statins

Model 1 was adjusted for none; Model 2 was adjusted for age, sex, BMI, smoking status, diabetes duration, Antihypertensive Drugs, Antiplatelet Drugs; Model 3 was adjusted for age, sex, smoking status, diabetes duration, Antihypertensive Drugs, Antiplatelet Drugs, eGFR, FBG, HbA1c, ALT, AST, TBIL, TG, LDL-C.

Table 5. Subgroup analysis

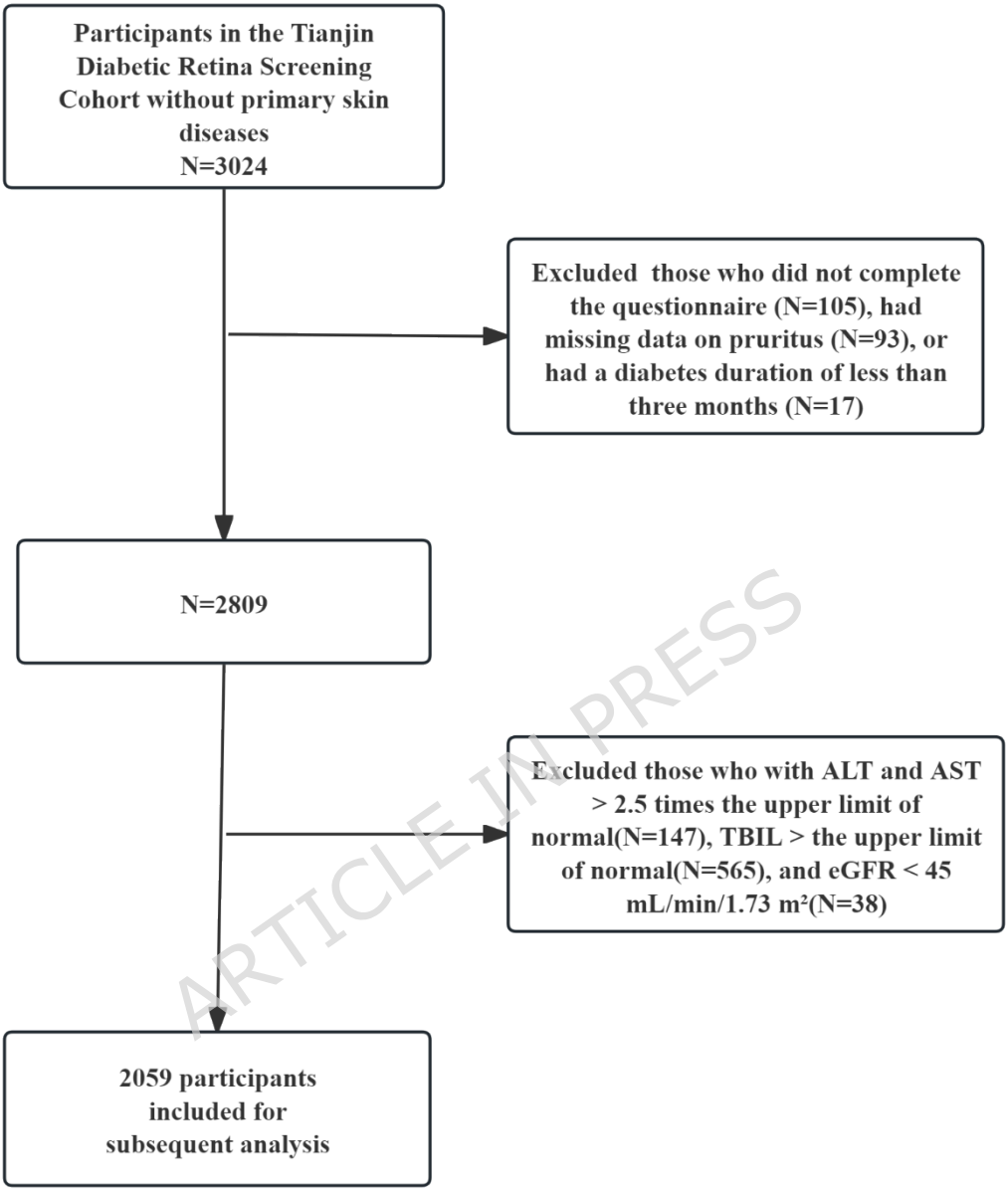
	Pruritus OR (95%)	P value	P for interaction
DPP-4is			
Sex			0.159
Female	1.13 (0.88–1.56)	0.376	
Male	1.61 (1.11–2.34)	0.019	
Age			0.439
<60	1.01 (0.07–10.25)	0.944	
≥60	1.31 (1.02–1.65)	0.032	
Diabetes Duration			0.145
<10	1.60 (1.09–2.35)	0.015	
≥10	1.11 (0.81–1.51)	0.521	
eGFR			0.431
45-60	1.09 (0.19–5.97)	0.922	
≥60	1.32 (1.03–1.69)	0.031	
Smoking status			
Never smoked,N(%)	1.27 (0.96–1.67)	0.094	REF
Current smoker,N(%)	1.63 (0.82–3.28)	0.164	0.852
Former smoker,N(%)	2.4 (0.78–8.09)	0.138	0.697
AGIs			
Sex			0.645
Female	1.25 (0.98–1.6)	0.056	
Male	1.23 (0.92–1.64)	0.132	
Age			0.071
<60	0.27 (0.06–1.07)	0.078	
≥60	1.34 (1.1–1.63)	0.003	
Diabetes Duration			0.471
<10	1.42 (1.05–1.92)	0.023	
≥10	1.18 (0.92–1.51)	0.201	
eGFR			0.024*
<60	6.4 (2.03–24.36)	0.003	
≥60	1.2 (0.99–1.46)	0.067	
Smoking status			
Never smoked,N(%)	1.28 (1.03–1.6)	0.027	REF
Current smoker,N(%)	0.96 (0.59–1.57)	0.886	0.275

Former smoker,N(%)	1.89 (0.78–4.72)	0.162	0.534
Statins			
Sex			0.397
Female	1.23 (0.95–1.59)	0.111	
Male	1.54 (1.11–2.13)	0.009	
Age			0.834
<60	1.38 (0.27–6.85)	0.691	
≥60	1.37 (1.11–1.68)	0.003	
Diabetes Duration			0.196
<10	1.25 (0.9–1.73)	0.185	
≥10	1.52 (1.17–1.98)	0.002	
eGFR			0.253
<60	2.31 (0.67–8.5)	0.192	
≥60	1.4 (1.14–1.72)	0.002	
Smoking status			
Never smoked,N(%)	1.4 (1.12–1.77)	0.003	REF
Current smoker,N(%)	2.27 (1.27–4.09)	0.006	0.132
Former smoker,N(%)	1.06 (0.39–2.89)	0.915	0.514

*P < 0.05, **P < 0.01, ***P < 0.001

Model was adjusted for DPP-4is,AGIs, Statins, Injectable Insulins, sex, BMI, smoking status, diabetes duration, Antihypertensive Drugs, Antiplatelet Drugs, FBG, HbA1c, ALT, AST, UACR, TG, LDL-C

Fig. 1. Patient screening and grouping



ALT, alanine aminotransferase; AST, aspartate aminotransferase; eGFR, estimated glomerular filtration rate; TBIL,total bilirubin