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Original article

Actinic keratosis and diabetes complications: A nationwide population-based study in South Korea (2009–2015)

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ABSTRACT

Aim. – As the associations between actinic keratosis (AK) and diabetes complications in patients with diabetes mellitus (DM) have never been investigated, this study aimed to evaluate any such associations in patients with DM.

Methods. – This retrospective cohort study analyzed clinical data for DM patients aged > 40 years who had undergone the health examination recommended by the South Korea National Health Insurance Program between 2009 and 2012 (n = 2,056,580). All of these patients were classified according to the presence of diabetic retinopathy (DR), end-stage renal disease (ESRD) and history of DVD; myocardial infarction, stroke, transient ischaemic attacks. Newly diagnosed AK was identified using claims data from baseline to the date of diagnosis or 31 December 2015, whichever came first.

Results. – Of the 2,056,580 patients with DM, 6404 (0.31%) developed AK. Those patients in the DR, ESRD and CVD groups were more likely to be diagnosed with AK ($P < 0.001$, by log-rank test). After adjusting for age and gender, the risks for AK were significantly higher in the DR, ESRD and CVD groups: HR (95% CI): 1.29 (1.21–1.39), HR: 4.24 (3.28–5.47) and HR: 1.22 (1.13–1.31), respectively.

Conclusion. – This study has revealed that the incidence of AK is higher in diabetes patients with ocular, renal and cardiovascular complications.

Introduction

Actinic keratosis (AK), which is among the most common dermatological diagnoses [1], is an inflammatory skin disorder involving proliferative and transformed keratinocytes on sun-exposed skin, especially the face. AK develops as a result of chronic ultraviolet exposure, and can lead to invasive squamous cell carcinoma (SCC). AK mostly affects elderly people with fair skin. Several reports have suggested that the incidence and economic burden of AK are both increasing [2,3]. The prevalence of actinic damage, including AK, was estimated to be 3.2%, with annual costs of $1.679 billion according to claims data from 2013 in the USA [4]. AK is clinically significant because it is a precancerous lesion that can lead to SCC.

Diabetes mellitus (DM) is a major chronic disease characterized by hyperglycaemia due to insulin insufficiency, the incidence of which has increased by 50% over the past 10 years [5]. The World Health Organization (WHO) has stated that 9.5% of the adult population had DM in 2008 [5]. Among the more devastating consequences of DM are a number of long-term micro- and macrovascular complications. Microvascular complications include retinopathy, nephropathy and neuropathy. Macrovascular complications include cardiovascular diseases (CVDs) such as myocardial infarction, stroke and transient ischaemic attacks (TIAs) [6]. These complications are responsible for much of the morbidity and mortality associated with DM.

Until now, the potential comorbidities of AK had never been investigated. As regards the medical burden of AK and the possibility of developing SCC, the association between AK and

Abbreviations: AK, actinic keratosis; ESRD, end-stage renal disease; CVD, cardiovascular disease.

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DM patients needs to be investigated. Indeed, it is our suspicion that there might be associations between AK and DM complications as agents such as photosensitizing drugs and immunosuppressive drugs, used in DM patients with complications, might be influencing the development of AK in these patients. However, there has been no study of the associations between AK and DM or its complications. For this reason, our present goal was to study the relationships between diabetes complications and AK in South Korea, using a nationally representative dataset and a long follow-up period.

Research design and methods

Data sources

This nationwide population-based retrospective cohort study used the National Health Insurance Service (NHIS) claims database, which contains all claims data for the National Health Insurance Program (NHIP), Medical Aid programme and all other long-term-care insurance programmes from 2009 to 2015. The NHIP is South Korea's universal healthcare system, which provides coverage for the entire country's population; numerous previous studies have proven the value of the NHIS claims database as a population-based dataset [7]. The database lists diagnoses by codes from the International Classification of Disease, Tenth Revision (ICD-10).

Study population

This study focused on DM patients aged > 40 years who underwent the recommended Korean health examination between 2009 and 2012. Patients were considered to have type 2 DM if they had one or more diagnoses while hospitalized or two or more diagnoses from outpatient clinic visits. Type 2 DM was diagnosed according to ICD-10 diagnostic codes (E11–E14) and the prescription of antidiabetic drugs (sulphonylureas, metformin, meglitinides, thiazolidinediones, dipeptidyl peptidase-4 inhibitors, α-glucosidase inhibitors and insulin).

The total number of Korean health examinations of type 2 DM patients (aged > 40 years) between 2009 and 2012 was 4,069,055. If a patient underwent multiple health examinations between 2009 and 2012 (n = 1,404,798), then data from only the first examination were included in the analysis. Those with missing data (n = 604,491) were excluded. The year in which patients first underwent the health examination was considered the index year for that subject. To avoid the confounding effect of preexisting AK, those who had a history of AK before the index year (n = 3186) were also excluded. Ultimately, the study population consisted of 2,056,580 DM patients, who were followed from baseline to the date of AK diagnosis or 31 December 2015, whichever came first. The study included all patients diagnosed with AK (ICD-10 code L570) by dermatologists during the study period (Fig. 1).

The study was approved by the Institutional Review Board (IRB) of the South Korean National Institute for Bioethics Policy (NHIS-2017-1-082) and the IRB of the Catholic University of Korea (Approval No. KC17ZESI0125). The IRB of the South Korea Centers for Disease Control and Prevention also approved the protocol. The study was conducted according to the principles of the Declaration of Helsinki. As only anonymized and de-identified information was used for the analyses, patients' informed consent was not required.

Data from medical health examinations

All enrollees in the South Korea National Health Insurance Corporation (NHIC) are recommended to undergo the standardized medical examination every 2 years. Data from these examinations were analyzed for all participants at baseline, and included measurements of height, weight, waist circumference, blood pressure, and laboratory tests such as for fasting glucose, total cholesterol, high-density lipoprotein (HDL) cholesterol and urinalysis. Past medical histories, including myocardial infarction, stroke and TIAs, and health-related behaviours such as smoking, drinking and physical activity levels, were collected using standardized self-reporting questionnaires. Quality-control procedures for the laboratory tests were performed in accordance with the South Korean Association of Laboratory Quality Control. Data for age and gender were obtained for all included patients. Smoking status was categorized as non-smoker, ex-smoker or current smoker, and alcohol drinking status was categorized as non-drinker, mild drinker (< 30 g/day) or heavy drinker (≥ 30 g/day) based on a question regarding frequency of alcohol consumption. Income level was dichotomized at the lowest 20%. Blood samples were drawn after an overnight fast and measured for serum levels of glucose, total cholesterol, blood urea nitrogen and creatinine. The hospitals in which the health examinations were performed were certified by the NHIS and, as such, were subject to regular quality control.

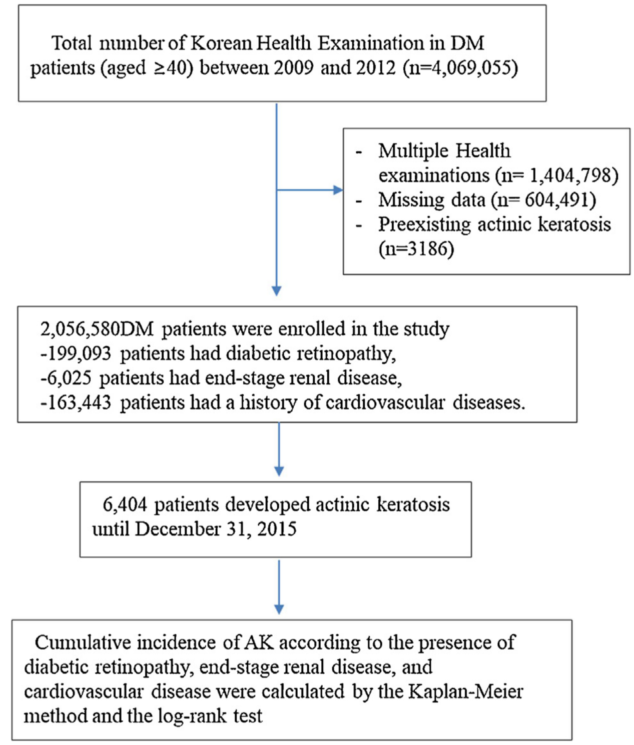

Fig. 1. Flow chart of patient inclusion in the study.

Presence/absence and definition of diabetes complications

To determine which complications are associated with AK, DM patients were classified according to the presence of three such complications at baseline: diabetic retinopathy (DR); diabetic nephropathy; and CVD. DR was defined by the appropriate diagnostic code (H360) in the NHIS dataset. The presence of diabetic nephropathy was identified by the diagnosis of end-stage renal disease (ESRD), or at least one claim per year under the ICD-10 codes N18, N19, Z49, Z905, Z94 and Z992, or the procedure codes for kidney transplantation and haemodialysis in the NHIS dataset. The CVD group was classified by their self-reported health-examination questionnaire response of a history of myocardial infarction, stroke or TIAs at baseline.

Definition of comorbidities

Baseline comorbidities were evaluated during the screening period (2009–2012), and their characteristics extrapolated from the ICD-10, prescription and procedure codes used for the medical claims. Also included were hypertension and dyslipidaemia. The presence of hypertension was defined as (1) at least one claim per year for prescription of an antihypertensive agent under ICD-10 codes I10–I15 or (2) systolic/diastolic blood pressure ≥ 140/90 mmHg. The presence of dyslipidaemia was defined as (1) at least one claim per year for prescription of an antihyperlipidaemic agent under ICD-10 code E78 or (2) a total cholesterol level ≥ 6.21 mmol/L.

Statistical analyses

Patients' baseline characteristics are presented as means ± standard deviations (SDs) or numbers and percentages. Incidence rates of AK were calculated by dividing the number of incident cases by the total follow-up period duration, and expressed per 1000 person-years. The cumulative incidence of AK according to the presence of DR, ESRD and CVD were calculated by the Kaplan–Meier method, and log-rank tests were used for comparisons between groups. Relative risk was expressed as the hazard ratio (HR) and 95% confidence interval (CI) using Cox proportional-hazards regression analysis, as did the supplemental analyses adjusted for baseline characteristics to evaluate the associations between the presence of diabetic complications and incidence of AK. The HR and 95% CI for each group relative to the reference were also calculated. Model 1 was adjusted for age and gender. Model 2 was adjusted for age, gender, smoking status, alcohol consumption, regular physical exercise and lowest income, and Model 3 was adjusted for age, gender, smoking status, alcohol consumption, regular physical exercise, lowest income, body mass index (BMI), hypertension, dyslipidaemia, glomerular filtration rate (GFR) and glucose levels. Statistical significance was defined as a two-sided P-value < 0.05. The Tukey method was used for multiple mean comparisons of different groups. Data were analyzed using SAS version 9.4 software (SAS Institute, Cary, NC, USA) and R programming, version 3.1.0 (The R Foundation for Statistical Computing, Vienna, Austria; http://www.R-project.org).

Results

Incidence of AK by presence/absence of DM complications

Of the included 2,056,580 type 2 DM patients, 6404 (0.3%) of them developed AK after a mean follow-up of 5.17 years. Those in the DR, ESRD and CVD groups were more likely to be diagnosed with AK than those in the non-DR, non-ESRD and non-CVD groups (all $P < 0.001$ by log-rank test; Fig. 2).

Patient demographics by presence/absence of DM complications

Of the 2,056,580 patients, 199,093 had DR, 6025 had ESRD and 163,443 had a history of CVD. According to the presence of these complications, patients were classified into DR and non-DR groups, ESRD and non-ESRD groups, and CVD and non-CVD groups. Their

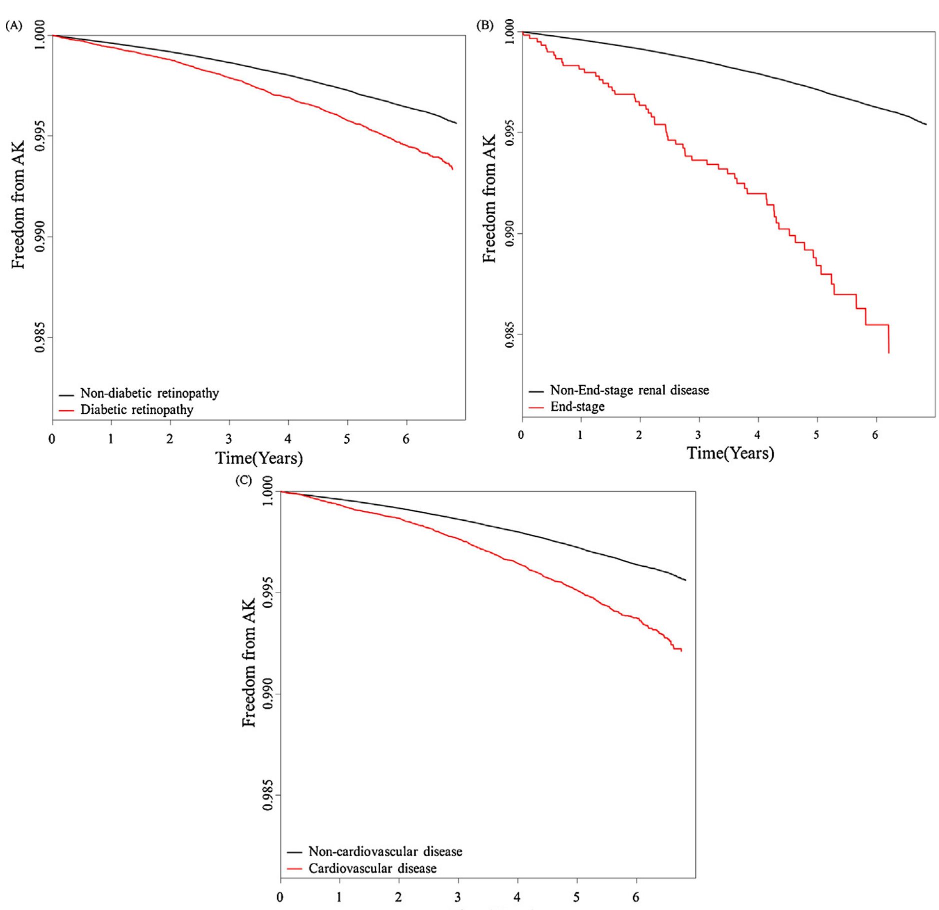

Fig. 2. Kaplan–Meier survival curves for no diagnosed actinic keratosis (AK) according to the presence/absence of: A. diabetic retinopathy. B. End-stage renal disease. C. Cardiovascular disease (all $P < 0.001$ by log-rank test).

Table 1
Demographics of type 2 diabetes patients according to the absence/presence of diabetes complications.

	Non-DR (n = 1,857,487)	DR (n = 2,050,555)	Non-ESRD (n = 2,050,555)	ESRD (n = 6025)	Non-CVD (n = 1,893,137)	CVD (n = 163,443)
DR		100	9.6	37	9.3	14
ESRD	0.20	1.1		100	0.27	0.59
CVD	7.6	12	7.9	16		100
Stroke	2.5	3.7	2.6	4.3		32
Heart attack	5.5	8.5	5.8	13		73
Age group						
< 60 years	53	36	51	47	54	24
≥ 60 years	47	64	49	53	46	76
Age (years)	57.9 ± 12.3	62.2 ± 9.7	58.3 ± 12.1	59.8 ± 10.1	57.7 ± 12.1	65.6 ± 9.5
Gender (male)	60	48	59	62	60	54
Smoking status						
Non-smoker	55	67	56	63	56	60
Ex-smoker	19	19	19	25	18	24
Current smoker	26	14	25	11	25	15
Alcohol consumption						
None	57	74	59	88	57	74
Mild (< 30 g/day)	34	22	33	11	34	22
Heavy (≥ 30 g/day)	9	4	8	1	9	4
Exercise	48	46	48	38	48	41
Lowest income (< 20%)	21[a]	22[a]	21	26	22	21
Hypertension	59	68	60	82	58	80
Dyslipidaemia	42	54	44	50	42	64
BMI (kg/cm^2)	25.1 ± 3.4	24.6 ± 3.2	25.1 ± 3.4	23.48 ± 3.3	25.1 ± 3.4	25.2 ± 3.3
Waist circumference (cm)	85.7 ± 8.6	84.9 ± 8.5	85.6 ± 8.5	83.7 ± 9.4	85.5 ± 8.5	86.6 ± 8.5
SBP (mmHg)	129.2 ± 15.6	128.4 ± 16.0	129.1 ± 15.7	133.9 ± 19.6	129.1 ± 15.6[c]	129.2 ± 16.3[c]
DBP (mmHg)	79.1 ± 10.1	76.8 ± 9.9	78.9 ± 10.1	77.8 ± 11.6	79.0 ± 10.1	77.5 ± 10.3
Glucose (mmol/L)	7.9 ± 2.4[b]	7.9 ± 2.8[b]	7.9 ± 2.4	7.5 ± 3.0	8.0 ± 2.4	7.5 ± 2.3
Total cholesterol (mmol/L)	5.1 ± 1.1	4.7 ± 1.1	5.1 ± 1.1	4.5 ± 1.1	5.1 ± 1.1	4.6 ± 1.1
HDL cholesterol (mmol/L)	1.3 ± 0.5	1.3 ± 0.5	1.3 ± 0.5	1.2 ± 0.4	1.3 ± 0.5	1.3 ± 0.4
GFR (mL/min/1.73 m^2)	84.7 ± 36.0	78.9 ± 35.4	84.3 ± 35.9	28.3 ± 31.8	84.8 ± 36.0	77.0 ± 35.4

Data are means ± SD or percentages. DR: diabetic retinopathy; ESRD: end-stage renal disease; CVD: cardiovascular disease; BMI: body mass index; SBP/DBP: systolic/diastolic blood pressure; HDL: high-density lipoprotein; GFR: glomerular filtration rate.
All $P < 0.001$ (comparing each pair of complications) except for:
[a] $P = 0.082$ for % difference of lowest income according to presence/absence of DR,
[b] $P = 0.989$ for mean difference in serum glucose according to presence/absence of DR,
[c] $P = 0.025$ for mean difference in SBP according to presence/absence of CVD.

baseline characteristics are presented in Table 1. Patients in the DR and CVD groups were significantly older than those in the non-DR and non-CVD groups, whereas the ESRD group was somewhat younger than the DR and CVD groups; the smallest gap in mean age was between the ESRD and non-ESRD groups. Also, the percentage of male patients was significantly larger in the ESRD group (62%).

Percentages of current smokers and mild-to-heavy drinkers were significantly lower in the DR, ESRD and CVD groups than in the non-DR, non-ESRD and non-CVD groups. The percentage of regular exercisers was significantly smaller in the ESRD group (38%) than in the non-ESRD group (48%).

While DM patients often have hypertension and/or dyslipidaemia as comorbidities, the ESRD and CVD groups had extremely high prevalences of hypertension (82% and 80%, respectively). The CVD group also had a high prevalence of dyslipidaemia (64%). In addition, DM patients are susceptible to obesity, with patients in the DR and ESRD groups having lower BMI scores (24.6 ± 3.2 kg/cm^2 and 23.5 ± 3.3 kg/cm^2, respectively), than the non-DR and non-ESRD groups (25.1 ± 3.4 kg/cm^2 and 25.1 ± 3.4 kg/cm^2, respectively).

Risk of AK in DM patients with or without complications

The incidence of AK was similar in the supplemental analyses of age, gender, BMI, hypertension and dyslipidaemia (Fig. 3). Variables significantly associated with AK were gender in the DR group and age in the ESRD group. Male patients were more strongly associated with AK (HR: 1.49, 95% CI: 1.35–1.64) than female patients (HR: 1.08, 95% CI: 0.98–1.20) in the DR groups ($P < 0.001$ for interaction; Fig. 3A), and those aged < 60 years in the ESRD group had a stronger association with AK (HR: 7.36, 95% CI: 4.91–11.01) than patients in the non-ESRD group aged > 60 years (HR: 2.83, 95% CI: 2.00–4.01, $P < 0.001$ for interaction; Fig. 3B).

Crude incidence rates of AK were 0.88, 2.27 and 1.01 per 1000 person-years in the DR, ESRD and CVD groups, respectively (Table 2). Results of the three different multivariate Cox proportional-hazards models showed that all three groups were significantly associated with the incidence of AK. After adjusting for age and gender (Model 1), the risk of AK was significantly higher in the DR, ESRD and CVD groups than in their null groups (HR: 1.29, 4.24 and 1.22, respectively). After further adjustments for confounding factors (Models 2 and 3), the higher HRs persisted. The ESRD group was more strongly associated with AK than were the DR and CVD groups (Table 2).

Discussion

Our present results carry the public-health implication that AK is associated with diabetes complications such as DR, ESRD and CVD, suggesting that more rigorous dermatological assessment of DM patients with complications may be necessary. In fact, reports have indicated that DM patients have an increased risk of several cancers. It has been suggested that persistent hyperglycaemia and high levels of insulin and insulin-like growth factors may contribute to malignant cell growth, while overexpression of superoxide dismutase and reactive oxygen species can lead to carcinogenesis in DM patients [8]. Cancers of the liver, pancreas, stomach, bowels, kidney, bladder, breast and endometrium have all been associated with DM [9,10]. Tseng et al. [11] showed that DM patients aged > 60 years had a significantly greater risk of

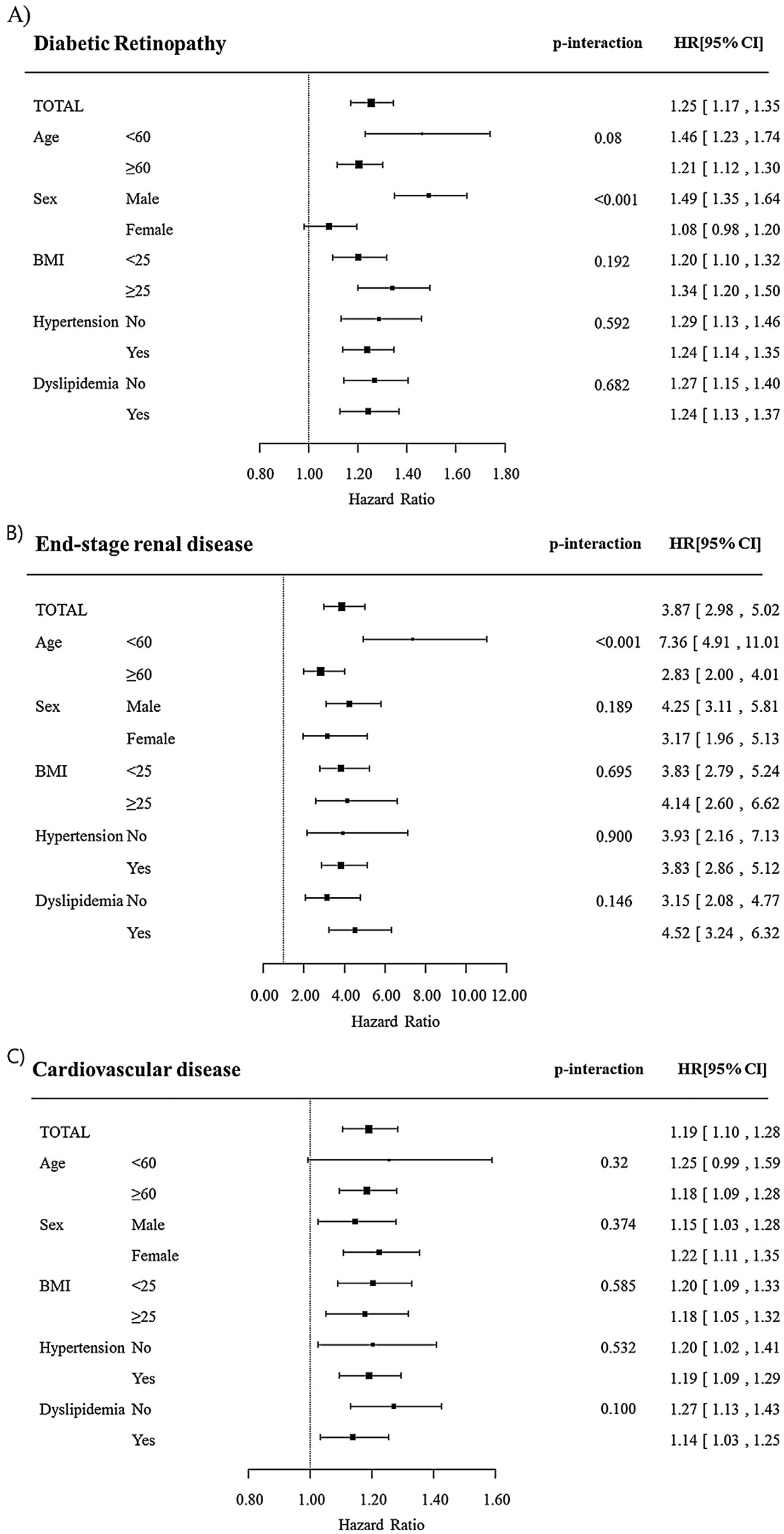

Fig. 3. Hazard ratios for actinic keratosis (AK) derived from subgroup analyses for age, gender, body mass index (BMI), hypertension and dyslipidaemia, after adjusting for glucose levels in: A. Diabetic retinopathy (DR). B. End-stage renal disease (ESRD). C. Cardiovascular disease (CVD) groups compared with non-DR, non-ESRD and non-CVD groups, respectively.

Table 2
Multivariate linear regression model of incidence rate and hazard ratio (HR) of diabetes complications according to diagnosis of actinic keratosis (AK; $n = 6404$).

	AK event	Person-years	Incidence rate (per 1000 person-years)	HR (95% CI)		
				Model 1[a]	Model 2[b]	Model 3[c]
DR						
No ($n = 1,857,487$)	5468	9,575,933.2	0.57	1 (reference)	1 (reference)	1 (reference)
Yes ($n = 199,093$)	936	1,055,355.2	0.89	1.29 (1.21–1.39)	1.27 (1.18–1.36)	1.26 (1.17–1.35)
ESRD						
No ($n = 2,050,555$)	6345	10,605,304.3	0.59	1 (reference)	1 (reference)	1 (reference)
Yes ($n = 6025$)	59	25,984.1	2.27	4.24 (3.28–5.47)	4.03 (3.12–5.21)	3.87 (2.98–5.02)
CVD						
No ($n = 1,893,137$)	5562	9,798,084.1	0.57	1 (reference)	1 (reference)	1 (reference)
Yes ($n = 163,443$)	842	833,204.3	1.01	1.22 (1.13–1.31)	1.2 (1.12–1.29)	1.19 (1.11–1.28)

DR: diabetic retinopathy; ESRD: end-stage renal disease; CVD: cardiovascular disease.
[a] Adjusted for age and gender.
[b] adjusted for age, gender, smoking status, alcohol consumption, exercise and lowest income.
[c] adjusted for age, gender, smoking status, alcohol consumption, exercise, lowest income, body mass index, hypertension, dyslipidaemia, glomerular filtration rate and glucose level.

non-melanoma skin cancer compared with a non-DM cohort. They also reported that, among DM patients, the significant risk factors for non-melanoma skin cancer were male gender and chronic obstructive pulmonary disease (COPD) and, for melanoma, coronary artery disease. Several other studies have also reported links between DM and non-melanoma skin cancer [12–14]. However, there have been no investigations of the associations between AK and other DM complications, making the present study the first to demonstrate a relationship between AK, a precancerous lesion, and such complications in DM patients.

Until now, only limited data have been available on risk factors of AK [15–17]. The Rotterdam Study [15] revealed that male gender, older age, light pigmentation status, severe baldness, wrinkled skin and a history of smoking are associated with actinic damage. Jacobs et al. [16] reported that several genes (*IRF4, MC1R* and *TYR*) are also risk factors for AK, and suggested that this was due to pleiotropic effects involving a combination of pigmentation and oncogenic functions. However, AK comorbidities have yet to be thoroughly investigated.

Many of the patients included in our study were considered overweight (mean BMI $\geq 25\ kg/cm^2$), and some studies have reported an increased risk of various cancers in obese individuals. The common explanation for cancer development in such people is that obesity is considered an inflammatory condition [18–20]. However, our study found that DM patients with ESRD were strongly associated with AK and yet had lower average BMI scores than the other DM patients. In fact, analysis of the BMI subgroups showed no significant differences in HRs for AK.

In the present study, ESRD was strongly associated with the development of AK, although this patient group was younger than either the DR or CVD group, and had lower rates of smoking and alcohol consumption, both of which are well-known protective factors against AK, but also reported less regular exercise, another protective factor. Nevertheless, the increased development of AK in the ESRD group might be explained by the immunosuppressive status of ESRD patients, as suggested by the increased incidences of AK and SCC in organ-transplant recipients receiving immunosuppressive therapy. Indeed, a previous study reported a 250-fold increase in the incidence of SCC in renal-transplant recipients compared with the general Dutch population [21]. Another possible explanation is that thiazide diuretics can cause photosensitivity. Photosensitizing drugs contain ingredients that can cause photosensitivity, defined as chemically induced skin changes that make people sensitive to light. Reactions to photosensitizing drugs involve photoallergy and phototoxicity, and exposure to ultraviolet light in combination with photosensitizing drugs may result in skin cancer and premature skin ageing. A large population-based, case–control study examined the effects of photosensitizing diuretics on SCC, based on data from the Danish Cancer Registry and the country's regional health service prescription database [22]. In addition, a recent European study showed a strong association between photosensitizing thiazide diuretics and AK [17]. Based on these previous studies, the ESRD patients in our study using photosensitizing diuretics or immunosuppressant drugs had an increased risk of AK.

DR is a well-known microvascular complication in type 2 DM patients [23]. Hyperglycaemia leads to intramural pericyte death and thickening of basement membrane, which contributes to changes in the integrity of blood vessels within the retina [24]. DR has been diagnosed in up to 25.2% of type 2 DM patients, and the rate is increasing [25]. Although the association between AK and DR is difficult to identify, the long-term use of photosensitizing antidiabetic drugs, including sulphonylureas, could be contributing to the increased risk for AK in DM patients with DR. Indeed, ours is the first study to reveal the association between DR and AK.

Furthermore, in our study, a history of CVD, arguably the most devastating consequence of DM, was also associated with AK. Based on previous reports, CVD medications might be influencing the development of AK [17,26]. Traianou et al. [17] found links between several medications and AK, and some potentially photosensitizing cardiac drugs were significantly associated with AK (HR: 4.56, 95% CI: 2.92–7.13). The possible culprit drugs include antihypertensive calcium-channel blockers, beta-adrenergic blockers, thiazide diuretics and angiotensin-converting enzyme (ACE) inhibitors. However, non-steroidal anti-inflammatory drugs (NSAIDs), commonly prescribed to CVD patients, had a negative association with AK. In fact, a preventative effect of NSAIDs against AK has been consistently reported [17,27,28]. These drugs are known to inhibit cyclooxygenase (Cox)-2, a potential mechanism for cancer prevention [27].

There are several limitations to our study. First, the diseases (DM, DR, ESRD, AK) were all indirectly inferred from claims data in the NHIS database. Second, the history of CVD in DM patients was obtained by self-reported questionnaires and, third, the severity of diabetes-related vascular complications was not considered. Fourth, other causes of ESRD were not evaluated and, finally, sun exposure and occupational information, which are associated with AK development, were not available in the NHIS database.

On the other hand, the strengths of our present study include the use of a large population-based data source, and the fact that this was the first-ever study to clarify the connection between AK and the development of DM complications. The database included AK patients with pathological diagnoses because, in South Korea, AK is diagnosed by dermatologists after a pathology examination. Another strength concerns the racial homogeneity of the South Korean population, which minimizes any bias due to racial differences.

In this nationwide cohort study, our findings have demonstrated that AK is associated with diabetes complications, including DR, ESRD and a history of CVD. Thus, physicians should pay more attention to monitoring cutaneous AK in DM patients, especially those with diabetes complications.

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Author contributions

Y.B.L. and J.H.L. searched the literature and wrote the manuscript. Y.B.L., J.H.L., J.Y.C. and D.S.Y. analyzed and interpreted the data. Y.B.L. and Y.G.P. devised the study concept and design. Y.G.P. and K.D.H. acquired the data. All authors contributed to the critical revision of the manuscript, and read and approved the final submitted version. Y.B.L. and Y.G.P. are the guarantors of this work and had full access to all the data in the study and, therefore, take full responsibility for the integrity of the data and accuracy of the data analysis.

Disclosure of interest

The authors declare that they have no competing interest.

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