

RESEARCH ARTICLE

Hypertension and risk of psoriasis incidence: An 11-year nationwide population-based cohort study

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Abstract

Psoriasis is a chronic inflammatory skin disease that is characterized by T-cell mediated immune response, and has been known to increase the risk of developing hypertension. However, the risk of psoriasis in patients with hypertension is not clear. Therefore, we investigated the risk of psoriasis in patients with hypertension. A total of 256,356 adults (42,726 in the hypertension group and 213,630 in the control group) were followed from 2003 to 2013 in a nationwide population-based cohort study. During the follow-up, 9,254 participants (3.6%) were found to have psoriasis (2,152 [5.0%] in the hypertension group and 7,102 [3.3%] in the control group). The hypertension group had a higher risk of psoriasis incidence (hazard ratio [HR] 1.54, 95% confidence interval [CI] 1.47–1.61, $P < 0.001$), and the association remained significant after adjusting for comorbidities of diabetes and dyslipidemia, antihypertensive medication and nonsteroidal anti-inflammatory drug use, and sociodemographic factors (HR 1.18, 95% CI 1.08–1.28, $P < 0.001$). In conclusion, hypertension was significantly associated with an increased risk of psoriasis incidence. Further studies are needed to confirm whether hypertension is associated with the incidence of psoriasis.

Introduction

Psoriasis is a chronic inflammatory skin disease related T-cell mediated immune mechanisms [1]. The prevalence of psoriasis is approximately 2% of the world's population [1], and is relatively lower in Asians, including Korea [2–5]. However, psoriasis has major effects on life since it is not only results in functional and social morbidities with socioeconomic cost [6], but also associated with an increased risk of various accompanying diseases [7,8]; thus, psoriasis has become a medical concern.

Hypertension, a well-known cardiovascular risk factor, contributes to the development of myocardial ischemia and infarction, stroke, and cardiovascular death [9]. Several studies have reported positive associations between psoriasis and hypertension [10,11]. Furthermore, most studies show that patients with psoriasis have a higher risk of hypertension [10,12]. However,

prospective studies investigating the association between hypertension and the risk of psoriasis development are rare. Wu et al. conducted a prospective study of the association between hypertension and the risk of psoriasis in US women [13], but no studies to date have evaluated the risk of psoriasis in men as well as women with hypertension.

Therefore, we investigated the association between hypertension and the prospective risk of psoriasis development using the National Health Insurance Service National Sample Cohort (NHIS-NSC) 2002–2013 that was produced by the Korean National Health Insurance Service (KNHIS).

Materials and methods

Ethical approval

The data used were extracted from the KNHIS claim database. All data were anonymized and provide us except for the patient's personal information. This study was approved by the Institutional Review Board of the KNHIS (NHIS-2016-2-213). In addition, the Ethics Committee of Seoul St. Mary's Hospital, the Catholic University of Korea approved this study design and a waiver of informed consent for the study (KC16EISE0524).

Data sources

In Korea, all of the nationals are obligated to enroll in the KNHIS, a nationwide health insurance system. Thus, the health system data are centralized in large databases. Medical providers are required to submit claims regarding diagnostic codes, procedures, prescription, the patient's personal information, and medical costs. The health care records of patients are not duplicated or omitted because all Korean nationals receive a unique identification number at birth, and the KNHIS uses the standard codes of the International Statistical Classification of Diseases and Related Health Conditions, 10th revision (ICD-10). This study used data from the NHIS-NSC 2002–2013, which were produced by the KNHIS using a proportionate stratified random sampling method based on 1476 strata according to age, sex, and household income to generate a nationally representative sample from a total of 46,605,433 Korean individuals in 2002. Therefore, the data comprised 1,025,340 subjects, which is approximately 2.2% of the entire Korean population.

The KNHIS converted all personal identification numbers into surrogate numbers before releasing the data file to researchers as a scrambled secondary data file to secure the privacy of insured persons.

Study population

The hypertension group included all patients initially diagnosed with hypertension (ICD-10: I10–I15) between January 2003 and December 2005 ($n = 110,393$). We excluded those patients aged < 20 years, those who were diagnosed with hypertension and/or psoriasis prior to enrollment, and those who had been diagnosed with psoriasis prior to their hypertension diagnosis and had a one-year washout period from January to December 2002 to reduce confounding of previously diagnosed hypertension. Finally, the hypertension group consisted of 42,726 subjects (23,383, 10,732, and 8,611 subjects in 2003, 2004, and 2005, respectively) who were considered new incident cases of hypertension. For the control group, 213,630 subjects (five per patient with hypertension) were selected from the database; they were matched to the patients with hypertension according to age and sex using propensity score matching. All of the included subjects were tracked on the basis of their health care records during the 11-year period from 2003–2013 to identify patients who developed psoriasis (ICD-10: L40).

Covariates

Information on age (20–39, 40–64, and ≥ 65 years), sex, residential area (urban area including Seoul city or rural area), household income ($\leq 30\%$ and $> 30\%$ of the median), use of antihypertensive medications including angiotensin-converting enzyme inhibitors, angiotensin receptor blockers (ARBs), β -blockers, calcium channel blockers (CCBs), and thiazides, and use of nonsteroidal anti-inflammatory drugs (NSAIDs) was obtained from the baseline. History of comorbidities including dyslipidemia and diabetes mellitus were defined as a diagnosis of these conditions between 2003 and 2013 prior to the diagnosis of psoriasis.

Statistical analysis

The characteristics of the study population according to hypertension status were analysed using the chi-squared test. Univariate and multivariate Cox proportional hazard regression analyses were conducted to identify the association between hypertension and the prospective development of psoriasis. A multivariate Cox proportional hazard regression analysis was used to adjust for comorbidities, antihypertensive medication and NSAID use, age, sex, residential area, and household income, which were obtained from baseline. Psoriasis-free survival was analysed using the Kaplan-Meier method for the 11-year follow-up period, and log-rank tests were performed to analyse the differences in psoriasis incidence between the hypertension and comparison groups. All of the statistical analyses were performed using the SAS software (version 9.4, SAS Institute, Cary, NC, USA). *P* values less than 0.05 were considered statistically significant.

Results

Characteristics of the study population

During the follow-up period, 9,254 psoriasis cases occurred among 256,356 subjects. [Table 1](#) shows the characteristics of the study population for the hypertension and comparison groups. The incidence of psoriasis in the hypertension group was higher than that in the comparison group (5.0% vs. 3.3%, $P < 0.001$). No differences in age, sex, or residential area were detected between the subjects with and without hypertension, but there were significant differences in the prevalence of diabetes and dyslipidemia, antihypertensive medication and NSAID use, and household income between the two groups.

Hypertension and other factors as predictors of psoriasis incidence

As shown in [Table 2](#), the group with hypertension had a higher risk of developing psoriasis (hazard ratio [HR] 1.54, 95% confidence interval [CI] 1.47–1.61, $P < 0.001$), and this association remained significant after adjusting for age, sex, household income, residential area, comorbidities of diabetes and dyslipidemia, NSAID use, and antihypertensive medication (HR 1.18, 95% CI 1.08–1.28, $P < 0.001$). The use of CCBs or thiazides was associated with a higher risk of psoriasis incidence after adjusting for the aforementioned covariates (HR 1.14, 95% CI 1.05–1.23, $P = 0.002$, and HR 1.10, 95% CI 1.02–1.18, $P = 0.010$, respectively).

Cumulative impact of hypertension on psoriasis incidence

The results of Kaplan-Meier curves for the psoriasis-free survival rate are shown in [Fig 1](#). The median follow-up duration was 9.7 years and 2,487,617 person-years were examined (409,565 person-years for the hypertension group and 2,078,052 person-years for the comparison group). Psoriasis occurred at rates of 10.5 and 6.8 per 1000 person-years in the hypertension

Table 1. Characteristics of the study population.

	Hypertension (n = 42,726)	Comparison (n = 213,630)	P
New-onset psoriasis	2,152 (5.0)	7,102 (3.3)	< 0.001
Year of hypertension diagnosis			-
2003	23,383 (54.7)	116,915 (54.7)	
2004	10,732 (25.1)	53,660 (25.1)	
2005	8,611 (20.2)	43,055 (20.2)	
Age (year)			0.798
20–39	4,317 (10.1)	21,585 (10.1)	
40–64	29,303 (68.6)	146,208 (68.4)	
≥ 65	9,106 (21.3)	45,837 (21.5)	
Male	21,912 (51.3)	109,867 (51.4)	0.587
Residential area (urban)	19,566 (45.8)	97,460 (45.6)	0.512
Low income ^a	6,618 (15.5)	43,488 (20.4)	< 0.001
Medication use			
ACEi	10,683 (25.0)	223 (0.1)	< 0.001
ARB	10,525 (24.6)	80 (0.04)	< 0.001
β-blocker	15,824 (37.0)	3,031 (1.4)	< 0.001
CCB	22,111 (51.8)	2,328 (1.1)	< 0.001
Thiazide	17,981 (42.1)	6,412 (3.0)	< 0.001
NSAID	29,946 (70.1)	110,986 (52.0)	< 0.001
Comorbidities			
Diabetes	5,933 (13.9)	7,172 (3.5)	< 0.001
Dyslipidemia	5,945 (13.9)	4,367 (2.2)	< 0.001

Values are expressed as n (%).

^aLow income is defined as household income ≤ 30% of the median.

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; NSAID, nonsteroidal anti-inflammatory drug.

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and comparison groups, respectively. Psoriasis occurred more frequently in the hypertension group than in the comparison group ($P < 0.001$ by log-rank test).

Subgroup analysis of the effects of hypertension on psoriasis incidence

The subgroup analyses of age and sex are shown in Table 3. Both males and females with hypertension had increased development of psoriasis after multivariate adjustments. The subjects with hypertension aged < 65 years had a higher risk of psoriasis development. Both male and female subjects with hypertension aged < 65 years had a higher risk of developing psoriasis, but males and females aged ≥ 65 years did not. ARB use was associated with a higher risk of psoriasis incidence among males aged < 65 years, and β-blocker use was associated with an increased risk of psoriasis among subjects aged ≥ 65 years. Associations were found between the use of CCBs or thiazides and the risk of psoriasis among females aged < 65 years.

Discussion

In this first large-scale cohort study, which included 42,726 subjects with hypertension and 213,630 matched controls, hypertension was positively associated with an increased risk of psoriasis development in the 11-year follow-up period, after adjusting for comorbidities of

Table 2. Longitudinal association between hypertension and psoriasis incidence.

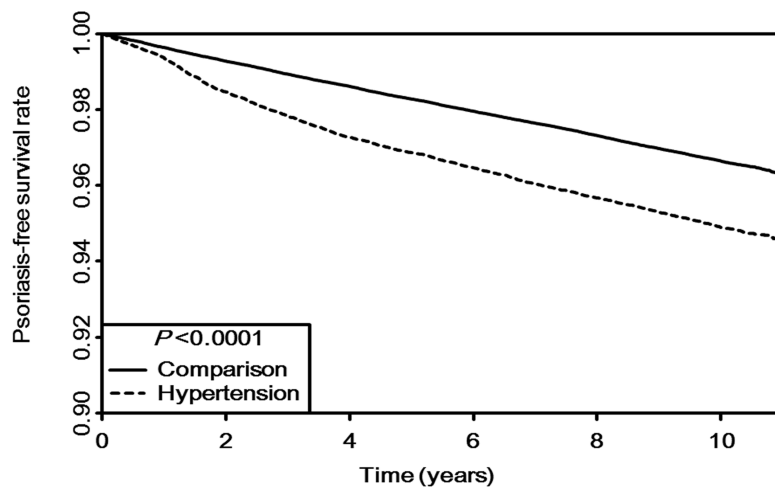
	Univariate Cox			Multivariate Cox ^a		
	HR	95% CI	P	HR	95% CI	P
Hypertension	1.54	1.47–1.61	< 0.001	1.18	1.08–1.28	< 0.001
Age (year)						
20–39	1			1		
40–64	1.35	1.24–1.45	< 0.001	1.32	1.22–1.43	< 0.001
≥ 65	1.26	1.16–1.38	< 0.001	1.27	1.16–1.39	< 0.001
Male	1.10	1.05–1.14	< 0.001	1.17	1.12–1.22	< 0.001
Antihypertensive medication						
ACEi	1.46	1.34–1.59	< 0.001	1.07	0.99–1.16	0.102
ARB	1.55	1.43–1.69	< 0.001	1.00	0.91–1.10	0.979
β-blocker	1.45	1.36–1.55	< 0.001	1.08	0.98–1.20	0.115
CCB	1.55	1.46–1.64	< 0.001	1.14	1.05–1.23	0.002
Thiazide	1.48	1.40–1.57	< 0.001	1.10	1.02–1.18	0.010
Diabetes	1.34	1.24–1.46	< 0.001	1.08	0.99–1.17	0.095
Dyslipidemia	1.64	1.51–1.78	< 0.001	1.28	1.17–1.40	< 0.001

^aMultivariate Cox regression analyses are adjusted for age, sex, household income, residential area, comorbidities of diabetes and dyslipidemia, current nonsteroidal anti-inflammatory drug use, and antihypertensive medication.

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; CI, confidence interval; HR, hazard ratio.

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diabetes or dyslipidemia, antihypertensive medication and NSAID use, and sociodemographic factors. In subgroup analysis according to sex and age, the causal association between hypertension and risk of psoriasis was similar, but hypertension in subjects aged ≥ 65 years was not associated with psoriasis incidence. CCB and thiazide use was associated with an increased risk of psoriasis incidence.



No. at risk						
Comparison	213630	212091	210672	209269	207895	114939
Hypertension	42726	42070	41556	41214	40873	22375

Fig 1. Kaplan–Meier survival curve. The overall psoriasis-free survival analyses for the hypertension and comparison groups are shown. The log-rank P value is significant, indicating a significant difference in psoriasis incidence between the hypertension and comparison groups.

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Table 3. Longitudinal association between hypertension and psoriasis incidence according to age and sex.

	Sex		Age		Age < 65 years		Age ≥ 65 years	
	Male	Female	< 65 years	≥ 65 years	Male	Female	Male	Female
Hypertension	1.14(1.01–1.29)	1.19(1.05–1.35)	1.20(1.09–1.32)	1.06(0.89–1.27)	1.16(1.01–1.33)	1.23(1.07–1.42)	1.06(0.82–1.37)	1.07(0.83–1.36)
Antihypertensive medication								
ACEi	1.09(0.98–1.25)	0.92(0.79–1.06)	0.99(0.89–1.11)	1.04(0.85–1.27)	1.09(0.93–1.26)	0.90(0.76–1.07)	1.12(0.84–1.50)	0.98(0.74–1.30)
ARB	1.19(1.04–1.36)	0.99(0.85–1.14)	1.05(0.94–1.18)	1.14(0.90–1.43)	1.17(1.01–1.37)	0.95(0.81–1.12)	1.22(0.87–1.70)	1.07(0.78–1.48)
β-blocker	1.09(0.97–1.22)	1.05(0.94–1.18)	1.03(0.94–1.13)	1.21(1.02–1.42)	1.06(0.93–1.20)	1.01(0.89–1.14)	1.22(0.96–1.56)	1.20(0.96–1.51)
CCB	1.11(0.99–1.24)	1.19(1.07–1.33)	1.20(1.09–1.31)	0.98(0.83–1.15)	1.18(1.01–1.30)	1.27(1.11–1.45)	0.98(0.77–1.23)	0.98(0.79–1.23)
Thiazide	0.98(0.87–1.09)	1.22(1.11–1.34)	1.14(1.05–1.24)	1.00(0.87–1.15)	0.99(0.88–1.13)	1.28(1.14–1.43)	0.92(0.74–1.14)	1.07(0.88–1.28)
Diabetes	1.07(0.95–1.19)	1.13(0.99–1.29)	1.07(0.96–1.18)	1.15(0.98–1.35)	1.03(0.90–1.18)	1.12(0.96–1.31)	1.16(0.93–1.45)	1.14(0.98–1.43)
Dyslipidemia	1.26(1.11–1.43)	1.31(1.16–1.49)	1.28(1.16–1.41)	1.34(1.09–1.64)	1.33(1.16–1.52)	1.21(1.05–1.40)	0.91(0.64–1.31)	1.68(1.31–2.15)

Values are expressed as hazard ratios (95% confidence interval). Cox regression analyses are adjusted for age, sex, household income, residential area, comorbidities of diabetes and dyslipidemia, nonsteroidal anti-inflammatory drug use, and antihypertensive medication.

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker.

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It has been widely reported that psoriasis is associated with metabolic components including diabetes, hypertension, and obesity. Psoriasis and these components may share similar risk factors such as chronic inflammation and oxidative stress, deviant angiogenesis, and specific genetic factors [14]. A number of previous studies have also reported that hypertension is positively associated with psoriasis [10,15–18]. Indeed, several biological pathways have been implicated in the association between psoriasis and hypertension including overexpression of endothelin in vascular endothelial cells and keratinocytes, increased oxidative stress, and common inflammatory mechanisms such as tumor necrosis factor and interleukin (IL)-17 [19–23]; however, previous prospective cohort studies investigating the association between hypertension and the risk of psoriasis development are rare [13]. Several studies have proposed a potential mechanism underlying the positive association between hypertension and the risk of psoriasis incidence. Cheng et al. showed that the *leucyl/cystinyl aminopeptidase (LNPEP)* gene was significantly downregulated in psoriasis lesions, and identified a coding variant of *LNPEP* in Chinese individuals with psoriasis, supporting the involvement of *LNPEP* in the etiology of psoriasis [24]. *LNPEP* (also known as angiotensin IV receptor), vasopressinase, and insulin-regulated aminopeptidase are aminopeptidases encoded by the *LNPEP* gene and are important components of the renin–angiotensin system pathway. A genetic variation in *LNPEP* was associated with plasma vasopressin clearance and serum sodium regulation [25], which play similar roles in the pathogenesis of hypertension and psoriasis. Furthermore, angiotensin IV, via angiotensin IV receptors, reportedly activates the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway and increases expression of pro-inflammatory genes [26], similar to the pathogenesis of psoriasis, which involves NF-κB and IL-23 signaling [27]. Elevated plasma renin and/or angiotensin-converting enzyme activities, which are associated with hypertension, were observed in psoriasis patients [28]. In addition, angiotensin II not only leads to the activation of physiological processes that contribute to increased blood pressure, but also stimulates T cell proliferation and promotes inflammation [29]; therefore, it may play an important role in the development of inflammatory and immune-mediated skin lesions in psoriasis.

The use of antihypertensive medications may be linked to increased incidence or exacerbation of psoriasis [30,31], but prospective studies concerning the causal relationship between antihypertensive medication use and psoriasis incidence are scarce. A previous prospective

study in 77,728 American women showed that long-term hypertensive status and use of β -blockers for 6 years or more were associated with a risk of psoriasis development [13]. In this study, CCB and thiazide use was associated with higher psoriasis incidence after adjusting for the abovementioned covariates, including hypertension status. Thus, use of CCB or thiazides might be a significant predictor of the development of psoriasis. In the subgroup analyses, however, among subjects aged < 65 years, not those aged ≥ 65 years, the associations were found between the use of CCB or thiazide and the risk of psoriasis. Therefore, further studies considering age or sex could be needed to confirm the association with antihypertensive medication use and psoriasis incidence.

In this study, subgroup analysis revealed that patients with hypertension aged < 65 years had a higher risk of developing psoriasis. Gelfand et al. showed that young patients with severe psoriasis have increased cardiovascular mortality compared with elderly individuals with severe psoriasis [32]. The increased prevalence of risk factors, including obesity, diabetes mellitus, or dyslipidemia, related to inflammation and oxidative stress increase the risk of hypertension development in younger adults [33], and these are similar to the pathologic conditions that contribute to the development of psoriasis [14], whereas the pathophysiology of hypertension in the elderly includes age-related changes such as elastic tissue degradation and the deposition of calcium in large conduit arteries [34]. Further investigations are warranted to clarify the effects of hypertension management including lifestyle modifications to decrease inflammation and oxidative stress on psoriasis incidence among hypertensive patients aged < 65 years.

The strengths of this study were that the data were collected through the 11-year longitudinal cohort and were based on a large sample size of 42,726 hypertensive patients and 213,630 controls. It is also the first cohort study to investigate the association between hypertension, antihypertensive medication use, and risk of psoriasis incidence in a representative nationwide sample of the South Korean population. However, this study had some limitations. Firstly, the diagnoses of hypertension, psoriasis, and comorbidities such as diabetes and dyslipidemia were identified using ICD-10 codes using claims databases. Therefore, coding errors and/or misclassification errors such as mismatching or misclassifying the target patients due to the nature of claims data could be possible. However, a validation study of the diagnostic codes of the KNHIS claims database revealed that approximately 70% of the diagnosis codes from the KNHIS claims records coincided with those from medical records [35]. Secondly, we were unable to stratify the baseline severity of hypertension for each patient, and information on psoriasis severity was not available in the claims database. Thirdly, we did not assess the dosage information or combination therapy of antihypertensive medication, which might be critical in determining the extent of psoriasis risk. Fourthly, some confounding factors, including weight, body mass index, and behavioral risk factors, such as smoking, alcohol consumption, and physical activity, were not available due to the limited clinical information present in the claims database.

In conclusion, the risk of psoriasis incidence was increased among patients with hypertension. A prior history of hypertension among subjects aged < 65 years, and CCB or thiazide use were associated with an increased risk of psoriasis incidence. These findings provide insights into the association between hypertension and the risk of psoriasis incidence. However, further studies are warranted to clarify whether hypertension is associated with the incidence of psoriasis.

Author Contributions

Conceptualization: Ha-Na Kim, Sang-Wook Song, Ji Hyun Lee.

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Formal analysis: Kyungdo Han.

Supervision: Sang-Wook Song, Ji Hyun Lee.

Writing – original draft: Ha-Na Kim.

Writing – review & editing: Ha-Na Kim, Sang-Wook Song, Ji Hyun Lee.

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