EnM
ENDOCRINOLOGY AND METABOLISM

Original Article

Endocrinol Metab 2022;37:770-780
https://doi.org/10.3803/EnM.2022.1519
pISSN 2093-596X · eISSN 2093-5978

Association among Current Smoking, Alcohol Consumption, Regular Exercise, and Lower Extremity Amputation in Patients with Diabetic Foot: Nationwide Population-Based Study

Yoon Jae Lee[1,*], Kyung-Do Han[2,*], Jun Hyeok Kim[1]

[1]Department of Plastic and Reconstructive Surgery, College of Medicine, The Catholic University of Korea; [2]Department of Statistics and Actuarial Science, Soongsil University, Seoul, Korea

Background: The present study investigates whether modifiable behavioral factors of current cigarette smoking, heavy alcohol consumption, and regular exercise are associated with risk of lower extremity amputation (LEA) in diabetic patients.

Methods: A total of 2,644,440 diabetic patients (aged ≥20 years) was analyzed using the database of the Korean National Health Insurance Service. Cox proportional hazard regression was used to assess adjusted hazard ratios (HRs) for the behavioral factors with risk of LEA under adjustment for potential confounders.

Results: The risk of LEA was significantly increased by current cigarette smoking and heavy alcohol consumption (HR, 1.436; 95% confidence interval [CI], 1.367 to 1.508 and HR, 1.082; 95% CI, 1.011 to 1.158) but significantly decreased with regular exercise (HR, 0.745; 95% CI, 0.706 to 0.786) after adjusting for age, sex, smoking, alcohol consumption, exercise, low income, hypertension, dyslipidemia, body mass index, using insulin or oral antidiabetic drugs, and diabetic duration. A synergistically increased risk of LEA was observed with larger number of risky behaviors.

Conclusion: Modification of behaviors of current smoking, heavy alcohol intake, and exercise prevents LEA and can improve physical, emotional, and social quality of life in diabetic patients.

Keywords: Smoking; Alcohol drinking; Exercise habits; Diabetic foot; Amputation risk assessment

INTRODUCTION

Diabetic foot is a chronic diabetic complication accompanied by peripheral neuropathy and vasculopathy due to complex metabolic pathways [1-3]. The incidence of diabetic foot was increased along with the incremental diabetes mellitus rate and the prolonged life expectancy of patients [2]. A lifetime incidence of foot ulceration in diabetic patients is 15% to 25% [4,5], and diabetic ulcer leads to poor quality of life [3,6,7] and high mortality [8,9]. Unfortunately, 28% of diabetic foot ulcers result in lower extrem-

Received: 27 May 2022, **Revised:** 13 August 2022, **Accepted:** 29 August 2022

Corresponding author: Jun Hyeok Kim
Department of Plastic Surgery, Yeouido St. Mary's Hospital, College of Medicine, The Catholic University of Korea, 10 63-ro, Yeongdeungpo-gu, Seoul 07345, Korea
Tel: +82-2-3779-1198, **Fax:** +82-2-780-9114, **E-mail:** hyeoggy@catholic.ac.kr

*These authors contributed equally to this work.

ity amputation (LEA) [10]. Five-year mortality rates have been estimated to be 42% to 44% after the onset of primary diabetic ulceration and increase to 68% to 79% after amputation [11,12].

In the USA, the average annual cost of diabetic foot is more than $8,500 per patient [13], and the medical cost for treating diabetic foot ranges from $9 to $13 billion more that the cost of diabetes itself [14]. A total cost for an LEA ranges from $43,800 (minor amputation, foot level) to $66,215 (major amputation, above ankle), and 77% of the costs are incurred after the amputation [15]. Diabetic foot incurs considerable social and medical burdens as well as economic costs for patients [16].

Various risk factors for LEA of age, sex, peripheral neuropathy, peripheral artery disease, glycated hemoglobin, hypertension, nephropathy, duration of diabetes, and obesity have been revealed [17-19] to affect a diabetic ulcer, its exacerbation, and the survival rate of diabetic patients.

The present study analyzed cohort data from the National Health Insurance Service (NHIS) in Republic of Korea to reveal whether modifiable behavioral factors of current cigarette smoking, heavy alcohol consumption, and regular exercise are associated with risk of LEA in patients with diabetic foot.

METHODS

Data source and study population

This study used the database of the NHIS, which enrolls approximately 97% of the Korean population through a biennial medical examination sponsored by the Korean government [20]. NHIS data can be used by researchers with official review board approval of the study protocol, as was received here.

Among 2,746,078 type 2 diabetic patients assigned to the NHIS between the years 2009 and 2012, the medical records of 2,745,688 individuals aged 20 years and over were evaluated until December 31, 2018. The presence of type 2 diabetes mellitus was defined according to the presence of at least one claim per year for prescription of diabetic medication under International Classification of Diseases 10th Revision (ICD-10) codes E11–E14 or fasting blood glucose ≥126 mg/dL. The primary endpoint of this study was newly amputated lower extremities, which were defined with the ICD-10 codes (N0571-5, N0562, N0564, N0565, and N0566). Patients with missing data, previous LEA, and 1 year lag were excluded. Fig. 1 shows a flow of the selection of the study population.

Data collection

Standardized self-reporting questionnaires were used to collect data to establish a baseline for the following variables regarded as risk factors for LEA and were included as covariates in the multivariate analyses: age (years); sex; cigarette smoking (never, former, and current); alcohol consumption (non, light, and heavy); level of physical activity; yearly income (lower quintile vs. the remaining quintiles); body mass index (BMI); diagnosis of hypertension, dyslipidemia, or chronic kidney disease (CKD); medication with insulin or oral antidiabetic drugs; and duration of diabetes. Systolic blood pressure and diastolic blood pressure were also obtained (mm Hg). Values for serum glucose (mg/dL), white blood cell (WBC) count (100/μL), total cholesterol, high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), and triglycerides (mg/dL) were also measured.

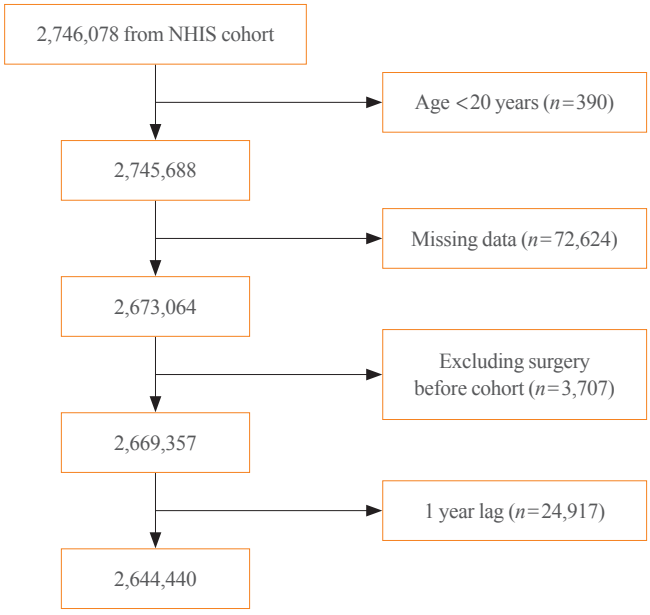

Fig. 1. Flowchart showing the enrollment process for the study cohort. NHIS, National Health Insurance Service.

In this study, the criteria for classifying alcohol consumption were defined on the basis of the daily pure alcohol intake on 360 mL of soju (Korean distilled liquor) with an alcohol concentration of 20%. The study population was divided into three groups: non-drinkers, light drinkers (alcohol consumption less than 30 g per day), and heavy drinkers (30 g or more grams per day).

The diagnosis of hypertension was defined as the presence of at least 1 claim per year for antihypertensive prescription under ICD-10 codes I10–I13 and I15 or systolic/diastolic blood pressure ≥140/90 mm Hg. The diagnosis of dyslipidemia was defined according to the presence of at least one claim per year for

antihyperlipidemic prescription under ICD-10 code E78 or a total cholesterol ≥6.21 mmol/L. The presence of CKD was defined as an estimated glomerular filtration rate <60 mL/min/1.73 m^2 calculated using the CKD Epidemiology Collaboration equation [21,22].

Informed consent was not obtained for this study because the study included routinely collected data. The study was approved by the Institutional Review Board of The Catholic Medical Center Office of Human Research Protection Program (SC21ZISE0165).

Statistical analyses

Statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA) and R version 3.2.3 (The R Foundation for Statistical Computing, Vienna, Austria, http://www.Rproject.org). All data are expressed as mean±standard deviation for normally distributed continuous variables and as proportion for categorical variables. The *t* test and analysis of variance (ANOVA) were used to analyze continuous variables, and the differences between nominal variables were compared with the chi-square test. The incidence rate of LEA in diabetic feet was calculated by dividing the number of events by person-time at risk. To determine the independent association of current cigarette smoking, heavy alcohol consumption, and regular exercise with risk of LEA in diabetic feet, the Cox regression model was used after adjusting for age, sex, smoking, alcohol consumption, regular exercise, low income, hypertension, dyslipidemia, BMI, using insulin or oral antidiabetic drugs, and diabetes duration. The cumulative incidence of LEA was plotted on a Kaplan-Meier curve. A two-sided *P* value <0.05 indicated a statistically significant difference.

RESULTS

Demographic characteristics

Table 1 shows the demographics of the study population according to LEA. Among a total of 2,644,440 diabetic patients, 0.33% (*n*=8,778) patients experienced LEA. The amputated patient group was generally older and included more men and more individuals who currently smoked; consumed alcohol heavily; did not exercise regularly; had limited income; had low BMI; were diagnosed with hypertension, dyslipidemia, and/or CKD; were treated with insulin or more than three oral antidiabetic drugs; and had higher serum glucose level/WBC count/

Table 1. Demographics of the Diabetic Foot Patients in the NHIS Cohort (2009 to 2012)

Variable	Total	Amputation		*P* value
		No	Yes	
Number	2,644,440	2,635,662	8,778	
Age, yr	57.41±12.33	57.39±12.33	61.57±10.78	<0.0001
20–40	200,993 (7.6)	200,778 (7.62)	215 (2.45)	<0.0001
40–65	1,647,984 (62.32)	1,643,131 (62.34)	4,853 (55.29)	
≥65	795,463 (30.08)	791,753 (30.04)	3,710 (42.26)	
Sex				<0.0001
Male	1,587,633 (60.04)	1,580,897 (59.98)	6,736 (76.74)	
Female	1,056,807 (39.96)	1,054,765 (40.02)	2,042 (23.26)	
Smoke				<0.0001
Non	1,472,125 (55.67)	1,467,988 (55.7)	4,137 (47.13)	
Ex	489,799 (18.52)	488,134 (18.52)	1,665 (18.97)	
Current	682,516 (25.81)	679,540 (25.78)	2,976 (33.9)	
Alcohol drink				<0.0001
Non	1,514,021 (57.25)	1,508,712 (57.24)	5,309 (60.48)	
Light	867,972 (32.82)	865,514 (32.84)	2,458 (28)	
Heavy	262,447 (9.92)	261,436 (9.92)	1,011 (11.52)	
Regular exercise	548,040 (20.72)	546,388 (20.73)	1,652 (18.82)	<0.0001
Limited income (25%)	611,073 (23.11)	608,708 (23.1)	2,365 (26.94)	<0.0001

(*Continued to the next page*)

Table 1. Continued

Variable	Total	Amputation		*P* value
		No	Yes	
BMI, kg/m^2	25.07±3.4	25.08±3.4	23.96±3.33	<0.0001
<18.5	41,569 (1.57)	41,269 (1.57)	300 (3.42)	<0.0001
<23	656,656 (24.83)	653,491 (24.79)	3,165 (36.06)	
<25	656,584 (24.83)	654,394 (24.83)	2,190 (24.95)	
<30	1,085,365 (41.04)	1,082,630 (41.08)	2,735 (31.16)	
≥30	204,266 (7.72)	203,878 (7.74)	388 (4.42)	
HP	1,499,654 (56.71)	1,493,541 (56.67)	6,113 (69.64)	<0.0001
DYS	1,107,349 (41.87)	1,103,509 (41.87)	3,840 (43.75)	0.0004
CKD	302,677 (11.45)	300,353 (11.4)	2,324 (26.48)	<0.0001
Retinopathy	87,647 (3.31)	86,667 (3.29)	980 (11.16)	<0.0001
Nephropathy	1,875 (0.07)	1,738 (0.07)	137 (1.56)	<0.0001
Cardio vasculopathy	111,181 (4.2)	110,510 (4.19)	671 (7.64)	<0.0001
Cerebral vasculopathy	45,368 (1.72)	44,984 (1.71)	384 (4.37)	<0.0001
Using insulin	162,226 (6.13)	160,322 (6.08)	1,904 (21.69)	<0.0001
More than three oral antidiabetic drugs	238,520 (9.02)	237,087 (9)	1,433 (16.32)	<0.0001
Diabetic duration over 5 years	818,864 (30.97)	813,019 (30.85)	5,845 (66.59)	<0.0001
Creatinine	0.9 (0.8–1.1)	0.9 (0.8–1.1)	1 (0.8–1.2)	<0.0001
Glucose, mg/dL	144.65±46.86	144.55±46.66	175.76±81.9	<0.0001
WBC, ×100/μL	85.43±8.65	85.43±8.65	85.84±8.68	<0.0001
SBP, mm Hg	129.03±15.82	129.02±15.81	131.48±18.33	<0.0001
DBP, mm Hg	79.05±10.27	79.05±10.27	78.76±11.1	0.0094
Total cholesterol, mg/dL	196.42±42.49	196.43±42.48	194.08±46.47	<0.0001
HDL-C, mg/dL	51.86±22.07	51.87±22.04	50.94±29.71	<0.0001
LDL-C, mg/dL	111.21±40.94	111.22±40.94	107.55±40.4	<0.0001
TG, mg/dL (geometric mean, 95% CI)	145.77 (145.67–145.87)	145.74 (145.64–145.84)	153.56 (151.7–155.44)	<0.0001

Values are expressed as mean±standard deviation, number (%), or median (interquartile range).
NHIS, National Health Insurance Service; BMI, body mass index; HP, hypertension; DYS, dyslipidemia; CKD, chronic kidney disease; WBC, white blood cell count; SBP, systolic blood pressure; DBP, diastolic blood pressure; HLD-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; TG, triglyceride; CI, confidence interval.

systolic blood pressure/triglycerides and low diastolic blood pressure/high-density lipoprotein/low-density lipoprotein than patients without LEA.

Risk of lower extremity amputation in diabetic foot according to current cigarette smoking, heavy alcohol consumption, and regular exercise

A multivariate analysis was performed with or without adjustment for age, sex, smoking, alcohol consumption, exercise, limited income, hypertension, dyslipidemia, BMI, use of insulin or oral antidiabetic drugs, and diabetes duration (Table 2). The risk of LEA increased with current cigarette smoking and heavy alcohol consumption (hazard ratio [HR], 1.436; 95% confidence interval [CI], 1.367 to 1.508 and HR, 1.082; 95% CI, 1.011 to 1.158), but it decreased with regular exercise (HR, 0.745; 95% CI, 0.706 to 0.786) after adjusting for the above variables.

A Kaplan-Meier curve also showed that a cumulative incidence of LEA in diabetic foot was heightened by current cigarette smoking and heavy alcohol consumption but was lowered by regular exercise (Fig. 2).

We assigned zero points if all three lifestyle habits were healthy, such as smoking cessation, no alcohol consumption, and regular exercise, adding one point for each worsening lifestyle choice and assigning three points for current smoking,

Table 2. Risk Factors and Hazard Ratios of the Risk of Amputation in Patients with Diabetic Foot

Variable	Number	Event	Duration	Incidence rate, /1,000 person-years	Hazard ratio (95% CI)	
					Non-adjusted	Adjusted[a]
Current cigarette smoking						
No	1,961,924	5,802	13,512,000	0.42940	1 (Reference)	1 (Reference)
Yes	682,516	2,976	4,630,204	0.64274	1.503 (1.438–1.571)[b]	1.436 (1.367–1.508)[b]
Heavy alcohol consumption						
No	2,381,993	7,767	16,346,859	0.47514	1 (Reference)	1 (Reference)
Yes	262,447	1,011	1,795,345	0.56312	1.187 (1.112–1.268)[b]	1.082 (1.011–1.158)[b]
Regular exercise						
No	2,096,400	7,126	14,317,538	0.49771	1 (Reference)	1 (Reference)
Yes	548,040	1,652	3,824,666	0.43193	0.865 (0.820–0.912)[b]	0.745 (0.706–0.786)[b]
Score[c]						
0	389,891	1,052	2,734,435	0.38472	1 (Reference)	1 (Reference)
1	1,583,446	4,859	10,856,128	0.44758	1.168 (1.092–1.248)[b]	1.366 (1.277–1.462)[b]
2	555,392	2,347	3,767,964	0.62288	1.631 (1.516–1.754)[b]	1.752 (1.562–1.966)[b]
3	115,711	520	783,677	0.66354	1.739 (1.566–1.932)[b]	2.448 (1.998–3.001)[b]

CI, confidence interval.
[a]Adjusted for age, sex, smoking, alcohol consumption, exercise, limited income, hypertension, dyslipidemia, body mass index, use of insulin or oral antidiabetic drugs, and diabetic duration; [b]A two-sided *P* value is under 0.05 indicated a statistically significant difference; [c]The score was 0 in the absence of all three lifestyle habits of smoking, drinking heavily, and not regularly exercising; one point was added for each unhealthy behavior, for a total of three points for smoking, heavy drinking, and not exercising.

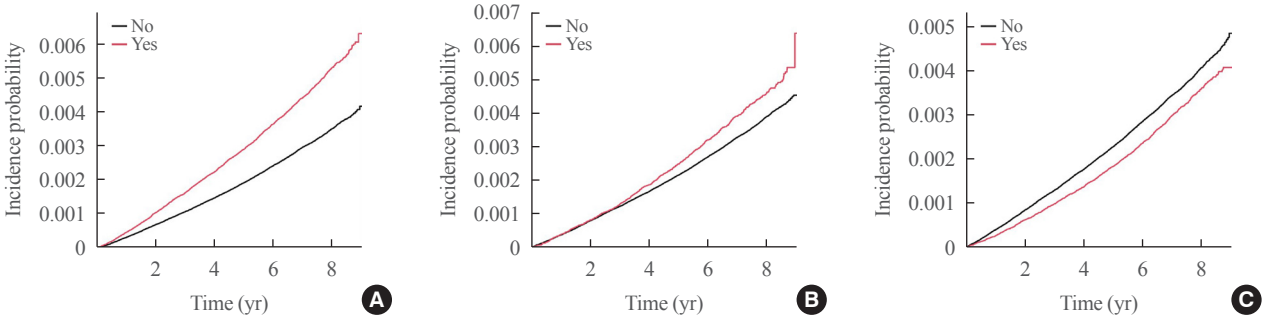

Fig. 2. Kaplan-Meier curves for cumulative incidence of lower extremity amputation in a diabetic population at biennial intervals. (A) Depending on current cigarette smoking. (B) Depending on heavy alcohol consumption. (C) Depending on regular exercise.

heavy drinking, and not exercising. After adjusting for the above-mentioned variables, the risk of LEA increased with every one-point increase (Score 1: HR, 1.366; 95% CI, 1.277 to 1.462; Score 2: HR, 1.752; 95% CI, 1.562 to 1.966; and Score 3: HR, 2.448; 95% CI, 1.998 to 3.001).

The effect of current cigarette smoking, heavy alcohol consumption, and regular exercise on amputation risk of diabetic foot according to amputation level

A multivariate analysis was performed according to the severity of amputation on diabetic foot. The severity of amputation was separated to minor amputation, foot level and major amputation, above ankle (Table 3). In the major amputation, the risk of LEA increased with current cigarette smoking (HR, 1.683; 95% CI, 1.487 to 1.905), but it decreased with regular exercise (HR, 0.638; 95% CI, 0.551 to 0.738) after adjusting for the above variables. However, correlation between heavy alcohol consumption and risk of LEA was not significant (HR, 1.012; 95% CI, 0.849 to 1.207; $P=0.8946$). Additionally, in the minor amputation, the risk of LEA increased with current cigarette smok-

Table 3. Risk Factors and Hazard Ratios of the Risk of Lower Extremity Amputation in Diabetic Foot according to Amputation Level

Variable	Number		Event		Hazard ratio (95% CI)			
					Non-adjusted		Adjusted[a]	
	Major	Minor	Major	Minor	Major	Minor	Major	Minor
Current cigarette smoking								
No	1,961,924	1,961,924	845	4,957	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
Yes	682,516	682,516	495	2,481	1.717 (1.537–1.918)[b]	1.467 (1.398–1.539)[b]	1.683 (1.487–1.905)[b]	1.394 (1.321–1.471)[b]
Heavy alcohol consumption								
No	2,381,993	2,381,993	1,191	6,576	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
Yes	262,447	262,447	149	862	1.141 (0.962–1.353)	1.196 (1.114–1.284)[b]	1.012 (0.849–1.207)	1.095 (1.018–1.179)[b]
Regular exercise								
No	2,096,400	2,096,400	1,121	6,005	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
Yes	548,040	548,040	219	1,433	0.729 (0.631–0.843)[b]	0.89 (0.840–0.943)[b]	0.638 (0.551–0.738)[b]	0.765 (0.722–0.811)[b]
Score[c]								
0	389,891	389,891	138	914	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
1	1,583,446	1,583,446	724	4,135	1.325 (1.105–1.59)[b]	1.144 (1.065–1.229)[b]	1.55 (1.289–1.864)[b]	1.338 (1.244–1.439)[b]
2	555,392	555,392	393	1,954	2.08 (1.713–2.525)[b]	1.563 (1.445–1.69)[b]	2.428 (1.785–3.304)[b]	1.655 (1.462–1.874)[b]
3	115,711	115,711	85	435	2.165 (1.653–2.837)[b]	1.675 (1.494–1.877)[b]	4.287 (2.481–7.408)[b]	2.226 (1.788–2.772)[b]

Major, amputation above ankle; Minor, foot level amputation; CI, confidence interval.
[a]Adjusted for age, sex, smoking, alcohol consumption, exercise, limited income, hypertension, dyslipidemia, body mass index, use of insulin or oral antidiabetic drugs, and diabetic duration; [b]A two-sided *P* value is under 0.05 indicated a statistically significant difference; [c]The score was 0 in the absence of all three lifestyle habits of smoking, drinking heavily, and not regularly exercising; one point was added for each unhealthy behavior, for a total of three points for smoking, heavy drinking, and not exercising.

ing and heavy alcohol consumption (HR, 1.394; 95% CI, 1.321 to 1.471 and HR, 1.095; 95% CI, 1.018 to 1.179), but it decreased with regular exercise (HR, 0.765; 95% CI, 0.722 to 0.811) after adjusting for the above variables. The above-mentioned scoring calculation, the risk of LEA increased with every one-point increase in both major and minor amputation.

The impacts of current cigarette smoking, heavy alcohol consumption, and regular exercise on risk of amputation in diabetic foot according to age, diabetic duration, and use of more than three oral diabetic drugs

The HRs of LEA by current cigarette smoking, heavy alcohol consumption, and regular exercise for age, diabetic duration, and use of more than three oral diabetic drugs are presented in Table 4. The risks of LEA increased more in older diabetic patients (65 years and older) than in younger diabetic patients (under 65 years) in those who were smoking and drinking heavily. On the other hand, the risk of LEA was reduced more in older diabetics (65 years and older) than in younger diabetics (under 65 years) in those who exercised regularly.

In terms of diabetic duration, current cigarette smoking and heavy alcohol consumption increased the risk of LEA, and the increase was greater in patients with a diabetes duration of 5 or fewer years compared to patients with duration longer than 5 years. However, the risk was reduced by a larger amount in patients with a duration longer than 5 years when they exercised regularly compared to such patients with a duration of 5 or fewer years.

The same pattern as in the duration of diabetes was seen in the use of more than three oral diabetic drugs. Current cigarette smoking and heavy alcohol consumption increased the risk of LEA more in patients using three or fewer oral diabetic drugs than in individuals treated with more than three oral diabetic drugs. However, regular exercise showed a greater reduction in

Table 4. Hazard Ratio for Risk of Amputation in Diabetic Foot according to Age, Diabetes Duration, and Oral Antidiabetic Drugs Stratified by Cigarette Smoking, Heavy Alcohol Consumption, and Regular Exercise

Subgroup	Current cigarette smoking		Heavy alcohol consumption		Regular exercise	
	Group	Hazard ratio (95% CI)[a]	Group	Hazard ratio (95% CI)[a]	Group	Hazard ratio (95% CI)[a]
Age, yr						
<65	No	1 (Reference)	No	1 (Reference)	No	1 (Reference)
	Yes	1.407 (1.323–1.496)	Yes	1.053 (0.971–1.141)	Yes	0.768 (0.716–0.824)
≥65	No	1 (Reference)	No	1 (Reference)	No	1 (Reference)
	Yes	1.522 (1.402–1.652)	Yes	1.185 (1.047–1.341)	Yes	0.702 (0.645–0.764)
Duration over 5 years						
No	No	1 (Reference)	No	1 (Reference)	No	1 (Reference)
	Yes	1.722 (1.587–1.869)	Yes	1.131 (1.020–1.255)	Yes	0.792 (0.720–0.871)
Yes	No	1 (Reference)	No	1 (Reference)	No	1 (Reference)
	Yes	1.29 (1.212–1.372)	Yes	1.038 (0.948–1.135)	Yes	0.719 (0.674–0.768)
More than three oral antidiabetic drugs						
No	No	1 (Reference)	No	1 (Reference)	No	1 (Reference)
	Yes	1.446 (1.370–1.526)	Yes	1.091 (1.014–1.174)	Yes	0.747 (0.704–0.792)
Yes	No	1 (Reference)	No	1 (Reference)	No	1 (Reference)
	Yes	1.384 (1.225–1.564)	Yes	1.050 (0.880–1.254)	Yes	0.728 (0.634–0.835)

CI, confidence interval.
[a]Adjusted for age, sex, smoking, alcohol consumption, exercise, limited income, hypertension, dyslipidemia, body mass index, use of insulin or oral antidiabetic drugs, and diabetic duration.

the risk in patients using three or fewer oral diabetic drugs compared to patients treated with more than three oral diabetic drugs.

DISCUSSION

Diabetic foot is a challenging and chronic complication that affects nearly 6% of patients with diabetes mellitus accompanied by peripheral neuropathy and peripheral arterial disease in the lower extremity due to complex metabolic pathways [1-3]. Its incidence has increased along with the growing prevalence of diabetes mellitus and the extended patient's lifespan [2].

An incidence of foot ulcer is up to 15% to 25% in diabetic patient's whole life [4,5]. The worldwide prevalence of diabetic ulcer is 6.3% [2], is highest in North America at 15% [23,24], and relatively low in Asia at 5.4% [25,26]. Diabetic ulcer impairs patients' quality of life [6,7], disturbs their social activity and existence [3], and contributes to high mortality [8,9]. The risk of death at 10 years after onset of diabetic ulcer is twice as high as that of those without diabetic ulcer [27]. Furthermore, 5-year mortality rates have been estimated to be 42% to 44% since primary diabetic ulceration and increase to 68% to 79% after amputation [11,12].

Diabetic ulcer usually develops in body areas subjected to repeated vertical or shear stress in a patient with peripheral neuropathy or peripheral artery disease [17,28]. Of the two, peripheral arterial disease is more likely to show diabetic ulcers progressing to nonhealing, infection, and even amputation [29].

About 40% of diabetic ulcers recur within 1 year after healing, 60% within 3 years, and 65% within 5 years [9]. One-third of diabetic foot ulcers result in LEA [10], and the rest heal conservatively [30]. Diabetes-related LEA rates are 0.04% to 1.5% [3,31]. In this study, the LEA rate of diabetic patients in Korea was 0.33%, but the proportion of diabetic feet among diabetic patients was unknown. In addition, although LEA, which is unrelated to diabetes, might be present in this study population, the effect on the statistical significance of the results would be negligible because the risk of an LEA with diabetes has been estimated at 23 times that without diabetes [32].

Various risk factors for LEA, including age, sex, peripheral neuropathy, peripheral artery disease, glycated hemoglobin, hypertension, nephropathy, longer diabetes duration, and obesity, have been shown to affect [17-19] early diagnosis, healing of a diabetic ulcer, exacerbation including infection and LEA, and

survival rate of diabetic patients. As Asian data about diabetic foot diseases are scarce [16], the present study analyzed whether modifiable behavioral factors of current cigarette smoking, heavy alcohol consumption, and regular exercise are associated with risk of LEA in Korean patients with diabetic foot.

Meta-analysis including five cohort studies and three case control studies demonstrated that cigarette smoking significantly increased the risk of LEA (odd ratio, 1.65; $P<0.0001$) without publication bias [33]. Smoking cessation also reduces the risk of LEA in diabetic foot, consistent with the results of the present study that current smoking increases the risk of LEA. Current smoking is the most potent but avoidable risk factor associated with cardiovascular, cerebrovascular, and peripheral vascular disease [34]. Its pathogenesis is reduced capacity to transport oxygen in the blood due to harmful by-products of cigarette smoking and results in tissue hypoxia and arteriospasm [35]. This damage leads to compensatory erythrocytosis that increases blood viscosity and decreases tissue perfusion [36]. Decreased tissue perfusion and oxygenation inhibit healing of diabetic ulcer, which can increase the risk of LEA.

Chronic and even regular moderate consumption of alcohol with diabetes results in hyperglycemia and peripheral neuropathy, contributing to development of diabetic ulcer, which can increase the risk of LEA [37]. This supports the results of the present study that heavy alcohol consumption enhanced the risk of LEA. Chronic alcohol consumption in diabetes tends to accompany poor compliance with diet and medication, which hampers glycemic control [38].

Six controlled clinical trials suggested that physical activity and exercise improved diabetic foot outcomes and prevented complications including diabetic ulcer, infection, and LEA [39]. The present study also indicated that regular exercise decreased the risk of LEA because physical activity and exercise in diabetic patients has improved glycemic control, nerve velocity conduction, and gait function [40,41]. Regular exercise in type 2 diabetic patients has resulted in positive glycemic control, which is effective in preventing diabetic peripheral neuropathy, a key risk factor of diabetic ulcers [42]. Exercise in diabetes patients increases both motor and sensory nerve velocity conduction of the lower limbs, with reduced distal latency [43]. It delays diabetic peripheral neuropathy and improves skin sensitivity and the vibration perception threshold [43,44]. In addition, diabetic patients who exercise regularly verified improved balance in one-legged posture; better foot rollover with redistribution of dynamic plantar loading; and improvement in quality of life [40,44]. Also, weight-bearing from physical activity is not associated with risk of diabetic foot re-ulceration [45].

The combination of smoking and chronic intake of alcohol in diabetic patients has demonstrated a higher rate of LEA and longer hospital stays [38]. The present study also indicated that addition of unhealthy behaviors increased the risk of LEA, with the highest risk for combined lack of exercise, current smoking, and heavy alcohol intake. A synergistically increased risk of LEA was observed with addition of each unhealthy behavior.

Diabetic foot occurs more frequently in male patients than in female patients [2]. The gender difference might be due to greater physical exertion in males [46]. This study also found a higher risk of LEA in males. However, vulnerability associated with current cigarette smoking and the beneficial effects of regular exercise showed a great impact on the risk of LEA in females.

The association between BMI and risk of diabetic foot ulceration is controversial [47,48] Recent studies revealed that higher risk of diabetic ulcer is related to a J-shaped BMI curve (BMI <25 kg/m^2 and BMI ≥ 45 kg/m^2) [49] or a specific range (BMI ranging from 25 to 30 kg/m^2) [2]. In the present study, low BMI (BMI <23 kg/m^2) and higher risk of LEA were associated in the Korean population. In addition, factors that enhanced the risk of LEA included older age; longer duration of diabetes; nephropathy; hypertension; and high levels of WBC, triglycerides, LDL-C, HDL-C, and serum C-reactive protein [50].

In the present study, older diabetic patients (65 years and older) showed higher risk of LEA with cigarette smoking and heavy alcohol intake than did younger patients, but the difference decreased with regular exercise. Patients with shorter diabetes duration (under 5 years) and a combination of three or fewer oral diabetic drugs were more susceptible to increased risk of LEA with smoking and heavy alcohol intake. In patients with diabetes duration longer than 5 years and use of more than three oral diabetic drugs, regular exercise was associated with a lower risk of LEA.

In conclusion, this nationwide population-based Korean study revealed that the risk of LEA in diabetic patients was increased by current cigarette smoking and heavy alcohol consumption but was reduced by regular exercise. A synergistically increased risk of LEA was observed with addition of each unhealthy behavior. Modification of behaviors including current smoking, heavy alcohol intake, and frequency of exercise is likely to decrease the incidence of LEA and improve the physical, emotional, and social quality of life in diabetic patients.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

ACKNOWLEDGMENTS

This research was supported by a grant of the Institute of Clinical Medicine Research in Yeouido St. Mary's Hospital, The Catholic University of Korea.

AUTHOR CONTRIBUTIONS

Conception or design: K.D.H., J.H.K. Acquisition, analysis, or interpretation of data: Y.J.L., K.D.H. Drafting the work or revising: Y.J.L., J.H.K. Final approval of the manuscript: J.H.K.

ORCID

Yoon Jae Lee *https://orcid.org/0000-0002-8376-9135*
Kyung-Do Han *https://orcid.org/0000-0002-6096-1263*
Jun Hyeok Kim *https://orcid.org/0000-0003-4657-2090*

REFERENCES

1. Apelqvist J. Diagnostics and treatment of the diabetic foot. Endocrine 2012;41:384-97.
2. Zhang P, Lu J, Jing Y, Tang S, Zhu D, Bi Y. Global epidemiology of diabetic foot ulceration: a systematic review and meta-analysis. Ann Med 2017;49:106-16.
3. Mishra SC, Chhatbar KC, Kashikar A, Mehndiratta A. Diabetic foot. BMJ 2017;359:j5064.
4. Lavery LA, Armstrong DG, Wunderlich RP, Tredwell J, Boulton AJ. Diabetic foot syndrome: evaluating the prevalence and incidence of foot pathology in Mexican Americans and non-Hispanic whites from a diabetes disease management cohort. Diabetes Care 2003;26:1435-8.
5. Reiber GE. The epidemiology of diabetic foot problems. Diabet Med 1996;13 Suppl 1:S6-11.
6. Jeffcoate WJ, Price PE, Phillips CJ, Game FL, Mudge E, Davies S, et al. Randomised controlled trial of the use of three dressing preparations in the management of chronic ulceration of the foot in diabetes. Health Technol Assess 2009;13:1-86.
7. Ragnarson Tennvall G, Apelqvist J. Health-related quality of life in patients with diabetes mellitus and foot ulcers. J Diabetes Complications 2000;14:235-41.
8. Kerr M, Rayman G, Jeffcoate WJ. Cost of diabetic foot disease to the National Health Service in England. Diabet Med 2014;31:1498-504.
9. Armstrong DG, Boulton AJM, Bus SA. Diabetic foot ulcers and their recurrence. N Engl J Med 2017;376:2367-75.
10. Armstrong DG, Lavery LA, Harkless LB. Validation of a diabetic wound classification system: the contribution of depth, infection, and ischemia to risk of amputation. Diabetes Care 1998;21:855-9.
11. Moulik PK, Mtonga R, Gill GV. Amputation and mortality in new-onset diabetic foot ulcers stratified by etiology. Diabetes Care 2003;26:491-4.
12. Ikonen TS, Sund R, Venermo M, Winell K. Fewer major amputations among individuals with diabetes in Finland in 1997-2007: a population-based study. Diabetes Care 2010;33:2598-603.
13. Ragnarson Tennvall G, Apelqvist J. Health-economic consequences of diabetic foot lesions. Clin Infect Dis 2004;39 Suppl 2:S132-9.
14. Rice JB, Desai U, Cummings AK, Birnbaum HG, Skornicki M, Parsons NB. Burden of diabetic foot ulcers for medicare and private insurers. Diabetes Care 2014;37:651-8.
15. Apelqvist J, Ragnarson-Tennvall G, Persson U, Larsson J. Diabetic foot ulcers in a multidisciplinary setting: an economic analysis of primary healing and healing with amputation. J Intern Med 1994;235:463-71.
16. Boulton AJ, Vileikyte L, Ragnarson-Tennvall G, Apelqvist J. The global burden of diabetic foot disease. Lancet 2005;366:1719-24.
17. Monteiro-Soares M, Boyko EJ, Ribeiro J, Ribeiro I, Dinis-Ribeiro M. Predictive factors for diabetic foot ulceration: a systematic review. Diabetes Metab Res Rev 2012;28:574-600.
18. Parisi MC, Moura Neto A, Menezes FH, Gomes MB, Teixeira RM, de Oliveira JE, et al. Baseline characteristics and risk factors for ulcer, amputation and severe neuropathy in diabetic foot at risk: the BRAZUPA study. Diabetol Metab Syndr 2016;8:25.
19. Papanas N, Maltezos E. Glycated hemoglobin as a risk factor for lower extremity amputations in diabetes: "success is counted sweetest". Int J Low Extrem Wounds 2015;14:106-7.
20. Lee J, Lee JS, Park SH, Shin SA, Kim K. Cohort profile: the National Health Insurance Service-National Sample Cohort (NHIS-NSC), South Korea. Int J Epidemiol 2017;46:e15.

21. Yang HK, Han K, Kwon HS, Park YM, Cho JH, Yoon KH, et al. Obesity, metabolic health, and mortality in adults: a nationwide population-based study in Korea. Sci Rep 2016; 6:30329.
22. Bae EH, Lim SY, Jung JH, Oh TR, Choi HS, Kim CS, et al. Chronic kidney disease risk of isolated systolic or diastolic hypertension in young adults: a nationwide sample based-cohort study. J Am Heart Assoc 2021;10:e019764.
23. Gulliford MC, Mahabir D. Diabetic foot disease and foot care in a Caribbean community. Diabetes Res Clin Pract 2002;56:35-40.
24. Adler AI, Boyko EJ, Ahroni JH, Smith DG. Lower-extremity amputation in diabetes: the independent effects of peripheral vascular disease, sensory neuropathy, and foot ulcers. Diabetes Care 1999;22:1029-35.
25. Riaz M, Miyan Z, Zaidi SI, Alvi SF, Fawwad A, Ahmadani MY, et al. Characteristics of a large cohort of patients with diabetes having at-risk feet and outcomes in patients with foot ulceration referred to a tertiary care diabetes unit. Int Wound J 2016;13:594-9.
26. Tseng CH. Prevalence and risk factors of diabetic foot problems in Taiwan: a cross-sectional survey of non-type 1 diabetic patients from a nationally representative sample. Diabetes Care 2003;26:3351.
27. Iversen MM, Tell GS, Riise T, Hanestad BR, Ostbye T, Graue M, et al. History of foot ulcer increases mortality among individuals with diabetes: ten-year follow-up of the Nord-Trondelag Health Study, Norway. Diabetes Care 2009; 32:2193-9.
28. Bus SA, van Deursen RW, Armstrong DG, Lewis JE, Caravaggi CF, Cavanagh PR, et al. Footwear and offloading interventions to prevent and heal foot ulcers and reduce plantar pressure in patients with diabetes: a systematic review. Diabetes Metab Res Rev 2016;32 Suppl 1:99-118.
29. Ward R, Dunn J, Clavijo L, Shavelle D, Rowe V, Woo K. Outcomes of critical limb ischemia in an urban, safety net hospital population with high WIfI amputation scores. Ann Vasc Surg 2017;38:84-9.
30. Apelqvist J, Larsson J, Agardh CD. Long-term prognosis for diabetic patients with foot ulcers. J Intern Med 1993;233: 485-91.
31. Lazzarini PA, Hurn SE, Fernando ME, Jen SD, Kuys SS, Kamp MC, et al. Prevalence of foot disease and risk factors in general inpatient populations: a systematic review and meta-analysis. BMJ Open 2015;5:e008544.
32. Holman N, Young RJ, Jeffcoate WJ. Variation in the recorded incidence of amputation of the lower limb in England. Diabetologia 2012;55:1919-25.
33. Liu M, Zhang W, Yan Z, Yuan X. Smoking increases the risk of diabetic foot amputation: a meta-analysis. Exp Ther Med 2018;15:1680-5.
34. Lakier JB. Smoking and cardiovascular disease. Am J Med 1992;93(1A):8S-12S.
35. Kourembanas S, Marsden PA, McQuillan LP, Faller DV. Hypoxia induces endothelin gene expression and secretion in cultured human endothelium. J Clin Invest 1991;88:1054-7.
36. Lee FS. Genetic causes of erythrocytosis and the oxygen-sensing pathway. Blood Rev 2008;22:321-32.
37. Ben G, Gnudi L, Maran A, Gigante A, Duner E, Iori E, et al. Effects of chronic alcohol intake on carbohydrate and lipid metabolism in subjects with type II (non-insulin-dependent) diabetes. Am J Med 1991;90:70-6.
38. Pal B, Raveender N, Sudipta P. A study on the impact of smoking and alcoholism as determinant factors in the prognosis and outcome of diabetic foot ulcer disease. Int J Res Med Sci 2016;4:1720-4.
39. Matos M, Mendes R, Silva AB, Sousa N. Physical activity and exercise on diabetic foot related outcomes: a systematic review. Diabetes Res Clin Pract 2018;139:81-90.
40. Sartor CD, Hasue RH, Cacciari LP, Butugan MK, Watari R, Passaro AC, et al. Effects of strengthening, stretching and functional training on foot function in patients with diabetic neuropathy: results of a randomized controlled trial. BMC Musculoskelet Disord 2014;15:137.
41. Tran MM, Haley MN. Does exercise improve healing of diabetic foot ulcers?: a systematic review. J Foot Ankle Res 2021;14:19.
42. Ang L, Jaiswal M, Martin C, Pop-Busui R. Glucose control and diabetic neuropathy: lessons from recent large clinical trials. Curr Diab Rep 2014;14:528.
43. Balducci S, Iacobellis G, Parisi L, Di Biase N, Calandriello E, Leonetti F, et al. Exercise training can modify the natural history of diabetic peripheral neuropathy. J Diabetes Complications 2006;20:216-23.
44. Ahn S, Song R. Effects of Tai Chi exercise on glucose control, neuropathy scores, balance, and quality of life in patients with type 2 diabetes and neuropathy. J Altern Complement Med 2012;18:1172-8.
45. Lemaster JW, Mueller MJ, Reiber GE, Mehr DR, Madsen RW, Conn VS. Effect of weight-bearing activity on foot ulcer incidence in people with diabetic peripheral neuropathy: feet first randomized controlled trial. Phys Ther 2008;88:

1385-98.
46. Moura Neto A, Zantut-Wittmann DE, Fernandes TD, Nery M, Parisi MC. Risk factors for ulceration and amputation in diabetic foot: study in a cohort of 496 patients. Endocrine 2013;44:119-24.
47. Pham H, Armstrong DG, Harvey C, Harkless LB, Giurini JM, Veves A. Screening techniques to identify people at high risk for diabetic foot ulceration: a prospective multicenter trial. Diabetes Care 2000;23:606-11.
48. Boyko EJ, Ahroni JH, Stensel V, Forsberg RC, Davignon DR, Smith DG. A prospective study of risk factors for diabetic foot ulcer: the Seattle Diabetic Foot Study. Diabetes Care 1999;22:1036-42.
49. Sohn MW, Budiman-Mak E, Lee TA, Oh E, Stuck RM. Significant J-shaped association between body mass index (BMI) and diabetic foot ulcers. Diabetes Metab Res Rev 2011;27:402-9.
50. Li X, Xiao T, Wang Y, Gu H, Liu Z, Jiang Y, et al. Incidence, risk factors for amputation among patients with diabetic foot ulcer in a Chinese tertiary hospital. Diabetes Res Clin Pract 2011;93:26-30.