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Increased risk of peripheral arterial disease in patients with alcohol intoxication: A population-based retrospective cohort study

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ABSTRACT

Previous studies have reported that light-to-moderate drinkers have a lower risk of peripheral arterial disease (PAD) than abstainers, and that heavy drinking increases the risk of PAD. However, reports of the effects of severe alcohol drinking on PAD are lacking within a population-based cohort. Alcohol intoxication is typically considered a medical emergency at clinics in Taiwan and is commonly attributed to excessive alcohol use. The present study aimed to investigate the association between alcohol intoxication and PAD risk. We conducted a retrospective, population-based, health insurance cohort study consisting of 56,544 adult patients with alcohol intoxication between January 1, 2000 and December 31, 2009, using claims data from the National Health Insurance Research Database (NHIRD) of Taiwan. This database included a control cohort of 226,176 residents without alcohol intoxication. The patients were age- and gender-matched. The incidence rate of PAD, after data regarding alcohol intoxication were obtained, was 12.8 per 10,000 person-years, and the adjusted hazard ratio (aHR) of PAD was 3.80 (95% confidence interval [CI] = 3.35–4.32, $p < 0.05$). The log-rank test showed that patients with alcohol intoxication had a considerably higher PAD cumulative incidence rate than those without alcohol intoxication. Alcohol intoxication was significantly associated with an increased risk of PAD in men (hazard ratio [HR] = 3.77, 95% CI = 3.30–4.31) and women (HR = 4.26, 95% CI = 2.60–6.97). The aHRs of PAD risk were 7.64 (95% CI = 4.39–13.3), 4.51 (95% CI = 3.83–5.29), and 2.16 (95% CI = 1.69–2.77) for patients with alcohol intoxication compared to participants of the control group aged <35 years, 35–64 years, and ≥65 years, respectively. The individuals with alcohol intoxication and without any comorbidities had a 3.77-fold increased risk of PAD in comparison to that of the control cohorts (HR = 3.77, 95% CI = 3.30–4.30). The aHR of PAD in patients with alcohol intoxication was 4.53 (95% CI = 2.51–8.16) in comparison to the control cohort, which consisted of patients with at least one existing comorbidity. Alcohol intoxication, along with the severe complications of excessive alcohol use, should be considered as major risk factors of PAD in the setting of a medical emergency. Further research needs to be performed to evaluate the quantitative effect of alcohol use on PAD.

List of abbreviations: CIs, confidence interval; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; HR, hazard ratio; LHID 2000, Longitudinal Health Insurance Database 2000; NHI, National Health Insurance; NHIRD, National Health Insurance Research Database; PAD, peripheral arterial disease; SD, standard deviation.

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Introduction

Peripheral arterial disease (PAD) is defined as an atherosclerotic disease of the non-cardiac vessels (Creager et al., 2012). The lower extremity vessels are affected more commonly than the upper extremity vessels. The worldwide prevalence of lower extremity PAD is between 3 and 12% (Creager et al., 2012; Hirsch et al., 2006a, 2006b; Novo, 2002; Olin & Sealove, 2010; Rooke et al., 2011; Tendera et al., 2011). Various abnormalities of vascular endothelial cells, smooth muscle cells, and platelets are linked to etiological factors of PAD (Kitta et al., 2009; Libby, Ridker, & Hansson, 2009). The most important risk factors involved are aging, smoking, diabetes mellitus, dyslipidemia, and hypertension (Félix-Redondo et al., 2012; Hirsch et al., 2001; Murabito, D'Agostino, Silbershatz, & Wilson, 1997; Selvin & Erlinger, 2004; Smith et al., 2004). In several previous epidemiological studies, the risk of PAD has been shown to be lower in light-to-moderate alcohol drinkers than in abstainers (Athyros et al., 2008; Camargo et al., 1997; Fabsitz et al., 1999; Jepson, Fowkes, Donnan, & Housley, 1995; Movva & Figueredo, 2013; Vliegenthart et al., 2002). The long-term burden of alcohol use has been considerably associated with the risk of PAD (Athyros et al., 2008; Rehm et al., 2003). In 2011, one animal study showed a controversial effect of daily-moderate and weekend-excessive alcohol consumption on atherosclerotic plaque development and highlighted the importance of patterns of alcohol consumption, as opposed to the total amount consumed, in relation to the cardiovascular effects of alcohol use (Liu, Redmond, Morrow, & Cullen, 2011). The pattern of excessive alcohol use has also been linked to risk of cardiovascular diseases (Roerecke & Rehm, 2010). The cardioprotective effect of low-risk patterns of alcohol use might disappear completely in the presence of excessive alcohol use (Roerecke & Rehm, 2010, 2011, 2012). Currently, the effect of excessive alcohol use, like alcohol intoxication, on PAD risk remains uncertain.

Alcohol intoxication is typically caused by excessive alcohol use, especially in binge drinking (Naimi et al., 2003; World Health Organization, 2014). Binge drinking is defined as an episode of excessive alcohol use in which the blood alcohol concentration level reaches 0.08% or more, which is commonly associated with the occasional consumption of four or more drinks for women or five or more drinks for men (Kanny, Liu, Brewer, & Lu, 2013). Approximately 38 million U.S. adults report binge drinking an average of four times per month, consuming an average of eight drinks per episode (Kanny et al., 2015). Worldwide, there are about 16% of drinkers aged 15 years or older who engage in heavy drinking (World Health Organization, 2014). Excessive alcohol use in patients that leads to alcohol intoxication may cause a differential, individual health burden on PAD risk. Therefore, the aim of this study was to investigate the association between alcohol intoxication, in the form of excessive alcohol use, and PAD risk.

Methods

Data source

We collected the data for this study from the National Health Insurance Research Database (NHIRD). The NHIRD was established by the National Health Research Institutes (NHRI) and contained data from the Taiwan National Health Insurance (NHI) program. The Taiwan NHI program has been a nationwide, single-payer health insurance provider since 1995. Because the Taiwan NHI program was compulsory for Taiwan citizens, the coverage rate of the Taiwan NHI was over 99% of the 23 million citizens who lived in Taiwan in 1998. The NHIRD contained comprehensive claims data from the Taiwan NHI program, including beneficiary registry disease records and other medical services. All the data were renewed every year. In this study, disease history of the insured people was collected from the inpatient files. The Taiwan NHI program constructed the disease record system based on the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). To safeguard the privacy of the insured people, the NHRI had a procedure for releasing the database that removed the original identification numbers and provided a scrambled, anonymous number to link each insured person's file. Furthermore, this study was approved by the Ethics Review Board of China Medical University (CMUH104-REC2-115-CR1). The IRB specifically waived the requirement for informed consent for the NHIRD application.

Study population

This study was a retrospective, population-based, health insurance cohort study. To interpret the association between alcohol intoxication and PAD risk, we selected an alcohol intoxication cohort and a comparison cohort and observed them. The selected alcohol intoxication cohort included patients with new-onset alcohol intoxication, whose diagnosis codes using the ICD-9-CM were 303, 305.0, and V113, between January 1, 2000 and December 31, 2009. We set the index date as the first diagnosed day. Based on the 1:4 matching, we randomly selected four control subjects who were without a history of alcohol intoxication per alcohol intoxication patients from the NHIRD and matched them for frequency by age, sex, and index year. We excluded participants with a history of PAD (ICD-9-CM 440.2, 440.3, 440.8, 440.9, 443, 444.22, 444.8, 447.8, and 447.9). The study participants started from the index date and ended when the participants either withdrew from health insurance, developed PAD, or until December 31, 2011.

We considered the confounding factors including age, sex, and PAD-associated comorbidity. The participants with comorbidity were defined as the participants with a disease history before the end of the follow-up period. PAD-associated comorbidities included hypertension (ICD-9-CM 401-405), hyperlipidemia (ICD-9-CM 272), diabetes (ICD-9-CM 250), atrial fibrillation (ICD-9-CM 427.31), chronic renal disease (ICD-9-CM 585), stroke (ICD-9-CM 430–438), heart failure (ICD-9-CM 428), ischemic heart disease (ICD-9-CM 410–414), chronic obstructive pulmonary disease (ICD-9-CM 490–496), cirrhosis (ICD-9-CM 571), and obesity (ICD-9-CM 278.0).

Statistical analysis

The mean and standard deviation (SD) were presented to describe ages, while numbers and percentages were presented to describe sex and comorbidity. To assess the distribution difference between the alcohol intoxication and the comparison cohorts, the *t*-test and chi-square test were performed for the continuous variable (age) and categorical variables (sex and comorbidity), respectively. The incidence density of developing PAD was calculated by the number of PAD events divided by the sum of observation time (per 10,000 person-years). The cumulative incidence curves for the two study cohorts were drawn using the Kaplan-Meier method, and we tested the curves' difference using the log-rank test. To present the PAD risk in patients with alcohol intoxication relative to the comparison participants, the crude hazard ratios (HRs), adjusted hazard ratios (aHRs), and 95% confidence intervals (CIs) were estimated using the Cox proportional hazards model. The multiplicative interaction between alcohol intoxication and sex and comorbidity for PAD risk were also estimated using the Cox proportional hazards model.

SAS 9.4 software (SAS Institute, Cary, NC, USA) was used for data management and statistical analysis, and the incidence curve was plotted using R software (R Foundation for Statistical Computing,