Joint Bone Spine 84 (2017) 189–196

Available online at ScienceDirect www.sciencedirect.com

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Original article

Alcohol-related diseases and alcohol dependence syndrome is associated with increased gout risk: A nationwide population-based cohort study

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ARTICLE INFO

Article history:
Accepted 13 February 2016
Available online 26 May 2016

Keywords:
Alcohol-related diseases
Alcohol dependence syndrome
Benzodiazepines
Gout

ABSTRACT

Objective: Alcohol intake is strongly associated with hyperuricemia, which may cause gout. This study evaluated the risk of gout in patients with alcohol-related diseases and alcohol dependence syndrome.
Methods: We used the Taiwan National Health Insurance Research Database (NHIRD) to conduct a nationwide population-based cohort study to assess the risk of gout and gout incidence in patients with alcohol-related diseases and alcohol dependence syndrome (as defined by the International Classification of Diseases, Ninth Revision). In the NHIRD records from 1998 to 2008, we identified 11,675 cases of alcohol-related diseases. The control group comprised 23,350 cases without alcohol-related diseases propensity score–matched (1 case: 2 controls) for age, age group, and sex.
Results: The results revealed that alcohol-related diseases were significantly associated with gout risk (adjusted hazard ratio 1.88; $P < 0.0001$). Of the alcohol-related disease cases, 34.1% of the patients had alcohol dependence syndrome (males 34.8%; females 32.4%), and alcohol dependence was independently associated with gout occurrence (relative risk [RR] 2.01; $P < 0.0001$). Severe alcohol-dependent patients (who were also the heavy benzodiazepines users), were associated with an increased risk of gout (RR 1.71 to 4.21, $P \leq 0.0182$).
Conclusion: Physicians should be aware of the association between alcohol dependence syndrome and gout occurrence, and alcohol use assessment and measures to prevent alcohol dependence should be implemented in the integrative care for patients with gout.

1. Introduction

Gout is the most common form of inflammatory arthritis, for which hyperuricemia, and consequently the intra-articular deposition of monosodium urate crystals, is a prerequisite [1]. The prevalence of gout in the US was 3.9% [2], 1.4–2.5% in the UK [3,4], 0.9% in France [5], 1.4% in Germany [3], 3.2% (European ancestry) to 6.1% (Māori ancestry) in New Zealand [6], and 4.62% (general populations) to 10.42% (aborigenes) in Taiwan [7,8]. Despite the availability of urate-lowering therapies in Taiwan, the prevalence of gout remains high compared with that in other countries.

Alcohol has been recognized as a potential risk factor for gout occurrence and is considered a trigger for acute gouty arthritis and recurrent gout attacks [9,10]. In addition, heavy alcohol consumption was associated with an increased risk of gout [9]. A prospective Internet-based case-crossover study reported that episodic alcohol consumption was associated with an increased risk of recurrent gout attacks [10]. A large prospective cohort study revealed that alcohol intake was strongly associated with increased gout incidence [9]. Moreover, metabolic studies have shown that alcohol consumption increases serum lactate levels, thus blocking renal excretion of urates [11,12]. These findings established that

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http://dx.doi.org/10.1016/j.jbspin.2016.02.024
1297-319X/

alcohol causes buildup of uric acid crystals in joints, eventually leading to gout.

Names of many conditions found in the International Classification of Diseases, Ninth Revision (ICD-9) reveal alcohol as the cause; example include alcoholic psychoses, alcoholic polyneuropathy, alcoholic cardiomyopathy, alcoholic gastritis, alcoholic fatty liver, acute alcoholic hepatitis, alcoholic cirrhosis of liver, alcoholic liver damage, alcohol dependence syndrome, and alcohol abuse. If various alcohol-related diseases differentially affect the risk of gout, it would have practical implications for gout prevention and management. The complex association between alcohol-related diseases and gout requires further investigation. Therefore, we conducted a nationwide population-based retrospective cohort study to evaluate how alcohol-related diseases affect the risk of gout; the study utilized the large data set of the National Health Insurance (NHI) program in Taiwan. In addition to investigating the association between alcohol-related diseases and gout, we investigated the presence of alcohol dependence in the records of patients with alcohol-related diseases receiving detoxification or withdrawal treatments, including the use of diazepam, chlordiazepoxide, oxazepam, and lorazepam.

2. Method

2.1. Data source

The NHI is a single-payer program in Taiwan established in 1995, covering over 98% of the population. Currently, the National Health Research Institutes in Miaoli, Taiwan, manage the National Health Insurance Research Database (NHIRD; www.nhri.org.tw/nhird/). The NHIRD is one of the largest nationwide population-based databases in the world and provides linked data, including patient demographic, registration data, diagnoses, prescriptions during hospital stays, outpatient claims data from hospitals and general practices, and the dispensing claims from hospitals, general practitioners, and community pharmacies, for epidemiological research [13]. The NHIRD has been used in numerous studies that have been published in peer-reviewed journals [13]. This study used the NHIRD Longitudinal Health Insurance Database (LHID) 2010, a nationally representative group of 1,000,000 beneficiaries who enrolled in the NHI in 2010, randomly sampled from the 2010 Registry for Beneficiaries of the NHIRD. LHID 2010 contains all original claims data from January 1, 2010, to December 31, 2010, of these beneficiaries (http://nhird.nhri.org.tw). Medical records from 1996 to 2010 of all selected individuals were analyzed in this study.

2.2. Study population

This study estimated the risk of gout following a diagnosis of alcohol-related diseases and alcohol dependence. The participants were followed from 1998 to 2010 (13 years) to assess the development of gout. In this retrospective cohort study, patients with and without first occurrence of alcohol-related diseases and gout were identified from the LHID 2010. In the linked data, all patient diagnoses were identified using the ICD-9 Clinical Modification (ICD-9-CM) codes. We analyzed the data to verify their eligibility as per the inclusion criteria.

The selection process of the study population is illustrated in Appendix A, Figure S1 (See the supplementary material associated with this article online). To avoid overestimating the incidence of gout, we excluded patients with a diagnosis of alcohol-related disease before January 1, 1998, and after January 1, 2009; if the development of gout correlates with the duration of the alcohol-related disease, including patients diagnosed with alcohol-related diseases before 1998 would result in overestimation of the risk of gout. We identified patients aged 20 and over who were alive as of December 31, 2010, as our study cohort. We excluded patients over 100 years of age, those not using gout medication (e.g., colchicine, xanthine oxidase inhibitor [allopurinol], and uricosuric agents [probenecid, sulfinpyrazone, and benzbromarone]), and those with 2 or fewer outpatient claims. In addition, we excluded patients who developed gout before the diagnosis of an alcohol-related disease. Furthermore, patients diagnosed with gout before December 31, 1998, were excluded to avoid overestimating the risk of gout in patients with alcohol-related diseases.

From the outpatient records from January 1, 1998, we identified 11,675 cases of alcohol-related diseases, diagnosed by a physician after 1998, including alcoholic psychoses (ICD-9-CM 291.x), alcohol dependence syndrome (303.x), alcohol abuse (305.0), alcoholic polyneuropathy (357.5), alcoholic cardiomyopathy (425.5), alcoholic gastritis (535.3), alcoholic fatty liver (571.0), acute alcoholic hepatitis (571.1), alcoholic cirrhosis of liver (571.2), alcoholic liver damage (571.3), and alcohol deterrents causing adverse effects in therapeutic use (E947.3) (Table 1). These subjects formed the alcohol-related diseases group. The control group comprised 23,350 subjects (1:2) who were propensity score–matched for age, age group, and sex (Appendix A, Figure S1). Appendix A, Table S1 presents the alcohol dependence patients receiving detoxification or withdrawal treatments, including the use of diazepam (Anatomical Therapeutic Chemical [ATC] code N05BA01), chlordiazepoxide (N05BA02), oxazepam (N05BA04), and lorazepam (N05BA06). The date of the first diagnosis for any alcohol-related disease was used as the index date for the alcohol-related diseases group, and January 1, 1998, was used as the index date for the control group. Subjects with gout were followed from the index date to the date of first diagnosis of gout. Subjects without gout were followed from the index date to December 31, 2010.

2.3. Outcomes and potential confounders

The outcome of interest in our study was a documentation of gout (ICD-9-CM code 274.x) by a physician or a rheumatologist in the outpatient claims. To enhance the accuracy of identifying the outcome of interest, we confirmed the diagnosis of gout by identifying in the diagnosis records at least one outpatient visit with a prescription of one or more gout medications (colchicine, xanthine oxidase inhibitor [allopurinol], and uricosuric agents [probenecid, sulfinpyrazone, benzbromarone]; Appendix A, Table S2).

We identified the potential confounders for gout in the study population: aboriginal living areas (yes/no), urbanization level (yes/no), socioeconomic status, and the Charlson comorbidity index (CCI) score. The CCI scores for the enhanced ICD-9-CM coding algorithm includes any condition that required 3 or more outpatient visits, as follows: myocardial infarction (1 point), congestive heart failure (1 point), peripheral vascular disease (1 point), dementia (1 point), chronic pulmonary disease (1 point), rheumatologic disease (1 point), peptic ulcer disease (1 point), diabetes mellitus (1 point uncomplicated), diabetes mellitus (2 points if end-organ damage), hemiplegia or paraplegia (2 points), renal disease (1 point), any malignancy (2 points), metastatic solid tumor (6 points), and AIDS (6 points) [14]. The CCI scores were categorized into four levels (0, 1–2, 3–4, and ≥ 5). Cases of mild liver disease (1 point) and liver disease (3 points if moderate to severe) were not included because alcohol-related diseases are related to liver diseases. The study project was reviewed and approved by the Institutional Review Committee of Kaohsiung Medical University Hospital (KMUHIRB-EXEMPT(I)-20150050), Taiwan.