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Benchmark dose of alcohol consumption for development of hyperuricemia in Japanese male workers: An 8-year cohort study☆

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ABSTRACT

Background: To estimate the benchmark dose (BMD) and their 95% lower confidence limits (BMDL) of alcohol consumption as the reference level for the development of hyperuricemia based on the dose−response relationship.

Methods: An 8-year prospective cohort study was conducted in 8097 male workers at a Japanese steel company who received annual health check-ups between 2002 and 2009. The endpoints for development of hyperuricemia were defined as a uric acid ≥7 mg/dL or taking any anti-hyperuricemic medication. The dose−response relationship of alcohol consumption was investigated using multivariate-pooled logistic regression analyses adjusted for other potential covariates. We estimated the BMD and BMDL of alcohol consumption for the development of hyperuricemia, using the parameters obtained by pooled logistic regression with a benchmark response (BMR) of 5% or 10%.

Results: Mean observed years per person was 3.86 years. The incidence rate per 1000 person-years was 61.1. The odds ratio calculated for the development of hyperuricemia was 1.29 [95% confidence interval, (1.22−1.36)] with an increase in alcohol consumption per 1 gou/day (1 gou/day = alcohol 22 g/day). The estimated BMDL/BMD with a BMR of 5% was 2.5/2.8 gou/day (54.5/61.8 g/day) and with a BMR of 10% was 4.0/4.6 gou/day (88.9/100.9 g/day).

Conclusions: The present study showed that alcohol consumption of 2.5 gou/day (=ethanol 55 g/day) caused a distinct increase in the risk of hyperuricemia. Valuable information for preventing alcohol-induced hyperuricemia was obtained by a long-term follow-up study of a large cohort.

Introduction

In general, an increase in serum uric acid (UA) level is associated with an increased risk of gout (Campion, Glynn, & DeLabry, 1987; Richette & Bardin, 2010), ureteral stones (Hall, Barry, Dawber, & McNamara, 1967; Yü & Gutman, 1967), kidney disease (Iseki et al., 2004; Weiner et al., 2008), hypertension (Campion et al., 1987; Krishnan, Kwoh, Schumacher, & Kuller, 2007; Lin, Lin, & Chou, 2000), coronary heart disease (Kim et al., 2010), and stroke (Kim et al., 2009). This indicates that the serum UA level is an important marker for preventing these diseases. Recent studies have shown that an elevated serum UA level is also associated with an increased risk of type 2 diabetes (Bhole, Choi, Kim, de Vera, & Choi, 2010) and the metabolic syndrome (Choi & Ford, 2007; Hjortnaes et al., 2007). However, there is considerable debate about whether or not hyperuricemia is a cause of other metabolic conditions. In a recent review, Mendelian randomization suggested that the observed relationship between serum urate level and ischemic heart disease is not a direct effect of urate (Robinson, Choi, Do, & Merriman, 2016).

On the other hand, alcohol consumption has been implicated in the etiology of hyperuricemia (Yamamoto, Moriwaki, & Takahashi, 2005). In a longitudinal epidemiologic study in the USA, alcohol consumption was shown to be associated with an increased risk of developing gout (Choi, Atkinson, Karlson, Willett, & Curhan, 2004). In addition, several epidemiologic studies based on cross-sectional observations (Gaffo et al., 2010; Gordon & Kannel, 1983; Teng et al., 2013) and prospective studies (Nakamura et al., 2012; Nakanishi,

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Yoshida, Nakamura, Suzuki, & Tatara, 2001; Uetani et al., 2006) indicated that excessive alcohol drinking had a harmful effect on hyperuricemia. However, as far as we are aware, the dose–response relationship between alcohol consumption and the risk of hyperuricemia and the threshold level of alcohol consumption has only been reported in one study (Nakamura et al., 2012).

In terms of calculating the threshold amount, the benchmark dose (BMD) method has attracted considerable attention in preventive medicine. The BMD method has become popular worldwide, especially in the area of preventive medicine. The concept of BMD was introduced by Crump (1984) and involves fitting a mathematical model to dose–response data. The BMD method has therefore been adopted by the U.S. Environmental Protection Agency (EPA) (1995) and Environmental Health Criteria (International Program on Chemical Safety, 2009) for assessing the health risk of environmental contaminants. The BMD is defined as the dose that causes a predetermined change in response (Sand, Victorin, & Filipsson, 2008). This specified change in response is generally referred to as the benchmark response (BMR) (Sand et al., 2008). The lower 95% confidence limit of the benchmark dose (BMDL) is increasingly replacing the no observed adverse effect level (NOAEL) for assessing risk (Sand et al., 2008; U.S. EPA, 1995). One major advantage of the BMD method over the NOAEL approach is that it uses information from the entire dose–response curve (U.S. EPA, 1995). Furthermore, using pooled logistic regression, it is possible to take into account the effect of potential covariates. From the viewpoint of preventive medicine, we consider that the threshold level of alcohol consumption calculated using this method is very important. However, as far as we are aware, previous studies have not estimated the BMDL for alcohol consumption and development of hyperuricemia. The aims of this study were to establish the dose–response relationship between alcohol consumption and the development of hyperuricemia and to estimate the BMD and BMDL of alcohol consumption for the development of this condition. This was achieved by applying pooled logistic regression analysis to data from an 8-year large-scale longitudinal cohort study in order to adjust for the annual variation in potential covariates. However, these data are specific for the Japanese population and lack generalizability to other populations.

Materials and methods

Participants

This cohort study at a Japanese steel company included observations made over an 8-year period from 2002 to 2009. A total of 8097 participants out of a possible 10,900 male workers were enrolled in the study. The cohort consisted of more than 98% of the workers who attended annual health examinations during the observation period. New participants could be enrolled during the follow-up period. The following individuals were excluded from the study: those who did not have a health examination in the subsequent year ($n = 1339$), those who did not have a UA measurement in the subsequent year ($n = 590$), those who were diagnosed with hyperuricemia based on the entry criteria in the present study ($n = 786$), and those with any missing data in the year of entry ($n = 88$). One hundred seventy-two workers out of a possible 10,900 male workers (1.57%) received urate-lowering therapy. In this company, serum uric acid of all workers was measured annually. Therefore, uric acid lowering therapy was generally started in the asymptomatic stages, and so we consider the actual prevalence of gout to be lower than this 1.57%. We did not exclude individuals taking diuretics because of the lack of this information in this cohort.

Measurements

Diagnosis of hyperuricemia was based on two data sources: the results of the annual health examination and individual medical histories. Health examination data included the results of a laboratory test for serum UA measured by the uricase–peroxidase reaction. The presence of hyperuricemia was defined as a UA $\geq$7 mg/dL or taking anti-hyperuricemic medication. The health examinations, including blood sampling, were carried out between 9:00 AM and 3:00 PM throughout the study period. None of the measurements was taken within 30 min after a meal or after heavy physical activity. The medical history of the workers was recorded during the annual health examination using a self-administered questionnaire. The responses were confirmed by individual interviews conducted by occupational physicians. Age, body mass index (BMI), blood pressure, and the levels of triglycerides, hemoglobin A_{1c} (HbA_{1c}), aspartate aminotransferase (AST), and creatinine (Cr) were measured during the study. The tests were conducted at comprehensive clinical testing laboratories that met the requirements of official certification organizations. Mean arterial pressure (MAP) was calculated using the following equation: ([diastolic blood pressure $\times$ 2] + systolic blood pressure)/3 (Meaney et al., 2000). Information on drinking and smoking habits, job schedule type, and habitual exercise was recorded at the annual health examination and obtained from self-administered questionnaires. Smoking status was classified as non-smoker, smoking 1–10 cigarettes/day, 11–20 cigarettes/day, or $\geq$21 cigarettes/day. The quantity of alcohol in each type of alcoholic beverage was calculated based on the unit "gou." In Japan, "gou" is the most popular unit used to measure alcohol consumption, with 180 mL of Japanese sake (rice wine) usually consisting of 15% ethanol. One gou (180 mL) of Japanese sake containing approximately 22 g of ethanol is equivalent to 500 mL of beer, 60 mL of whiskey, 180 mL of wine, or 110 mL of shochu (Japanese distilled spirits). This unit was used in the questionnaire, as it is easily comprehensible for the general Japanese population to determine their consumption of alcohol beverages. To calculate the total quantity of alcohol consumed per day, we assigned a score to each category as follows: 0 for 0 gou, 0.5 for <1 gou, 1 for about 1 gou, 2 for about 2 gou, 3 for about 3 gou, and5 for $\geq$4 gou. Weekly alcohol consumption was estimated by multiplying the quantity by the frequency. The weekly alcohol consumption was then converted to daily consumption and expressed as two units (gou/day and ethanol g/day). The other variable factors were categorized as follows: Job schedule type (daytime or shift work) and habitual exercise (none, once-twice/month, once-twice/week, or 3 times/week or more).

Statistical analyses

To evaluate the dose–response relationships between annual measurements of alcohol consumption and the development of hyperuricemia, we used multivariate analysis that included pooled logistic regression (D'Agostino et al., 1990). All the covariates were included simultaneously in the statistical model. Using this method, the derived-odds ratios (ORs) for the endpoints were adjusted for the effects of the other time-variable covariates. The data on triglycerides, HbA_{1c}, AST, and Cr were logarithmically transformed using a base of 1.5. This transformation resulted in the ORs for the variables increasing by 50%. Each examination interval of one year was treated as a mini follow-up study. This method therefore included the concept of person-years. The daily alcohol consumption was used as a continuous variable to estimate the BMDL and BMD. The BMDL and BMD were adjusted for the effects of the other covariates using parameters obtained by pooled logistic regression.