Chapter 5

Is alcohol consumption truly protective for developing rheumatoid arthritis?

Diane van der Woude*, Annekoos L. Huidekoper*, Rachel Knevel, Annette H.M. van der Helm-van Mil, Suzanne C. Cannegieter, Frits R. Rosendaal, Margreet Kloppenburg and Tom W.J. Huizinga

** These authors contributed equally*

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ABSTRACT

Objective To evaluate the association between alcohol consumption and the risk of developing rheumatoid arthritis (RA) and other forms of arthritis.

Methods Included were patients participating in the Leiden Early Arthritis Cohort with RA (n=651), other forms of arthritis (reactive arthritis, spondylarthropathy or psoriatic arthri tis, n=273), osteoarthritis (OA, n=73), as well as 5877 general population controls. Odds ratios were calculated by logistic regression analysis. Subgroup analysis was performed, stratified for antibodies to citrullinated peptide antigens (ACPA) status (n=257) compared to patients with other forms of arthritis (n=273). Subset analyses were performed on remission data and radiographic progression.

Results Alcohol consumption was associated with a reduced risk of RA (OR 0.27 (95%CI 0.22-0.34)), of other forms of arthritis (OR 0.34 (95%CI 0.24-0.48)) and OA (OR 0.31 (95%CI 0.16-0.62)). The degree of systemic inflammation, reflected by the level of erythrocyte sedimentation rate (ESR), was inversely associated with alcohol consumption. There was no dose-response relationship between the amount of alcohol consumed and the risk of arthritis. ACPA-positive RA patients reported less alcohol consumption than patients with other forms of arthritis (OR 0.59 (95%CI 0.36-0.99)). Adjustment for the ESR-level slightly changed this risk (OR 0.63 (95%CI 0.38-1.07)). No association between alcohol consumption and rate of joint destruction or remission was seen.

Conclusion Arthritis patients report less alcohol consumption than controls, regardless of the type of arthritis. The largest part of this association is not specific for RA, but subgroup analysis shows that there may a particularly protective effect of alcohol consumption towards ACPA-positive RA.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, inflammatory disease which is characterized by persistent inflammation and joint destruction. It has previously been shown that environmental risk factors such as smoking may interact with genetic factors in predisposing to the development of RA characterized by the presence of antibodies to citrullinated peptide antigens [1-5]. Smoking habits and drinking habits are associated. It is of interest to evaluate the possible effect of alcohol consumption on the risk of developing RA.

Several reports have suggested a compromising effect of ethanol on both innate and adaptive immunity [6, 7] with downregulation of proinflammatory cytokines and increase of anti-inflammatory cytokines [8-11]. Moreover, experimental studies with collagen-induced arthritis in mice have shown an anti-inflammatory and anti-destructive effect of ethanol consumption by interaction with innate immune responsiveness [12].

The association between alcohol consumption and RA has been evaluated in several previous reports [13-17], but no definite conclusions could be drawn. Recently, a report comprising Swedish and Danish data on alcohol consumption in reference to development of RA indicated that there may be a dose-dependent protective effect of alcohol [18]. Our objective was to evaluate whether there is an inverse association between alcohol consumption and the risk of developing arthritis, and more specifically in relationship to the presence of RA with antibodies to citrullinated peptide antigens (ACPA). By inclusion of several arthritic case groups, we investigated whether the effect of alcohol is specific for RA. The latter has never been evaluated in previous studies.

METHODS

Patient and control population

We performed a case-control analysis in which cases were participants in the early arthritis cohort (EAC) from the Leiden University Medical Center, the Netherlands. This cohort consists of patients presenting with arthritis to the outpatient clinic, who were subsequently diagnosed with various different forms of arthritis. Cases that were included in the analyses were recruited between February 1993 and December 2008 and were older than 18 years of age. Patients were diagnosed with RA according to the 1987 criteria of the American College of Rheumatology [19]. Patients with other forms of arthritis were selected from the EAC cohort based on a definite diagnosis of reactive arthritis, spondylarthropathy, psoriatic arthritis or osteoarthritis (OA).

A total of 5877 non-arthritic controls were selected from the Multiple Environmental and Genetic Assessment of risk factors for venous thrombosis study (MEGA trial). This group consisted of patients with a first diagnosis of venous thrombosis. Between March

1999 and September 2004 patients were selected from files of the anticoagulation clinics in Amsterdam, Amersfoort, the Hague, Leiden, Rotterdam and Utrecht. This group has been described in detail elsewhere [20]. A group of 3297 partners of patients with venous thrombosis were included in our study. From January 2002 to September 2004 an additional number of 3000 random control subjects were recruited in the MEGA study and used in our study. Only control subjects with no recent history of venous thrombosis were included. Patients with severe psychiatric problems or those unable to speak Dutch were considered ineligible. All control subjects selected were older than 18 years of age. Both cohorts were approved by the medical ethical committee.

Data collection

Alcohol consumption was recorded at baseline, at first presentation to the outpatient clinic. In the EAC cohort, information on alcohol and smoking was initially obtained by means of an interview by a trained research nurse when patients first presented to the outpatient clinic. After December 2002, data were collected by self-administered questionnaires. A modified Stanford Health Assessment Questionnaire (HAQ) was filled in and the disease activity score in 44 joints was assessed (DAS44) [21].The control subjects in the MEGA trial were sent questionnaires to fill in at home. Cases and controls with missing data on alcohol consumption where excluded in our analyses.

The questions asked about alcohol- and smoking habits in both cases and controls were comparable. Data on alcohol consumption were dichotomized as current or non-drinker. Additionally, the amount of alcohol consumption was categorized into four groups, based on the quartiles of percentages in the control population: non-drinkers; low consumption; moderate consumption and high consumption. The data on smoking were divided in current/previous or non-smokers.

Statistical analysis

Statistical analysis was performed using SPSS version 16.0 (SPSS Inc, Chicago, Ill). To compare the distribution of baseline characteristics in the groups, Kruskal-Wallis-, Chi-square- and t-tests were performed. The effect of alcohol consumption on the risk of developing disease was analyzed by univariate and multivariate logistic regression. Relative risks are expressed as odds ratios with 95% confidence intervals based on the standard errors derived from the model. The latter analysis was adjusted for age, sex and body mass index (BMI) and smoking since these were possible confounders. Separate analyses were executed based on diagnosis, ACPA-status and the type of healthy control (partners vs random controls). Pearson's chi-square test was used for analyzing the association between alcohol consumption and the level of erythrocyte sedimentation rate (ESR). P-values less than 0.05 were considered significant for all statistical tests. Subset analyses were performed on remission data and radiographic progression. Sustained

DMARD-free remission was defined as fulfilling the following criteria for at least one year: 1) no current DMARD-use, 2) no swollen joints and 3) classification as remission by the patient's rheumatologist [22]. For remission data a Cox-regression analysis was performed. Data on radiographic progression with a follow-up duration of 7 years, were evaluated using a repeated measurement (linear multivariate regression) model [23, 24] corrected for smoking, ACPA-status, sex, age, HAQ, DAS44, delay (time between onset of symptoms and first visit to the outpatient clinic) and baseline Sharp-van der Heijde score.

RESULTS

Alcohol consumption and risk of RA and other forms of arthritis

A total of 651 RA patients, 346 patients with other forms of arthritis (273 patients with reactive arthritis, spondylarthropathy or psoriatic arthritis, 73 patients with osteoarthritis (OA)) and 5877 healthy controls were included. The baseline characteristics are shown in Table 1. Patients with RA or OA were older and more often female than patients with other forms of arthritis and the healthy controls. The BMI differed between the group of

Table 1. Baseline characteristics of patients and controls.

Characteristic	RA, n=651	OA, n=73	Other arthritis, n=273 *	Controls, n=5877	P-value (Kruskal-Wallis)
Age (in yrs), mean (SD)	56.5 (16)	64.0 (12)	44.4 (15)	47.3 (13)	<0.001
Female gender, n (%)	435 (67)	56 (77)	123 (45)	3158 (54)	<0.001
BMI (in kg/m^2), mean (SD)	25.9 (4)	26.4 (4)	25.7 (4)	25.6 (4)	0.018
Symptom duration (in months), mean (SD)	6.8 (10)	9.1 (17)	5.8 (11)	----	<0.001
ESR (in mm/h), mean (SD)	39 (26)	22 (21)	34 (31)	----	<0.001
ACPA-positive, n (%)	257 (54%)	3 (7%) #	15 (10%) #	----	<0.001

* Spondylarthropathy, psoriatic arthritis, reactive arthritis: P-values are listed for the comparison between two cohorts, using t-tests for normally distributed continuous variables and Chi-square tests for dichotomous variables.
Age of RA patients vs healthy controls: p-value <0.001
Age of osteoarthritis patients vs healthy controls: p-value <0.001
Age of other arthritis patients vs healthy controls: p-value <0.001
Sex of RA patients vs healthy controls: p-value <0.001
Sex of osteoarthritis patients vs healthy controls: p-value <0.001
Sex of other arthritis patients vs healthy controls: p-value 0.005
BMI of RA patients vs healthy controls: p-value 0.058
BMI of osteoarthritis patients vs healthy controls: p-value 0.230
BMI of other arthritis patients vs healthy controls: p-value 0.650
ACPA was measured in 43 of 73 osteoarthritis patients and 157 of the 273 "other arthritis" patients.
Abbreviations: RA: rheumatoid arthritis, OA: osteoarthritis, BMI: body mass index.

OA patients and the group of healthy subjects, therefore these possible confounders were included in subsequent multivariate analyses.

Table 2 lists the number of patients and controls that reported drinking alcohol. Odds ratios (OR) were adjusted for age, sex, BMI and smoking due to the known association between smoking and drinking habits. This analysis shows a substantially reduced risk of all forms of arthritis associated with alcohol consumption. A subanalysis performed within in the group of cases included after December 2002 (when patients where given self-administered questionnaires), showed that the cited amount of alcohol consumption was not influenced by how the data on alcohol consumption were collected.

Table 2. Number of individuals drinking alcohol by diagnosis versus healthy controls

Diagnosis	Cases, n (%)	Healthy controls n = 5877, n (%)	OR *	95% CI *	p
RA, n=651	362 (56)	4901 (83)	0.27	0.22-0.34	<0.001
Total other arthritis n=273	175 (64)	4901 (83)	0.34	0.24-0.48	<0.001
• **SpA, n= 76**	44 (58)	4901 (83)	0.34	0.17-0.67	0.002
• **Arthr.Ps., n=130**	89 (69)	4901 (83)	0.38	0.23-0.62	<0.001
• **React. Arthr, n=67**	42 (63)	4901 (83)	0.27	0.14-0.52	<0.001
Osteoarthritis, n=73	39 (53)	4901 (83)	0.31	0.16-0.62	0.001

* 95% Confidence interval adjusted for age, sex, BMI, smoking
RA= rheumatoid arthritis, SpA= spondylarthropathy, Arthr. Ps.= psoriatic arthritis, React. Arthr.= reactive arthritis, BMI= body mass index, OR= odds ratio.

Dose-response relationship

When alcohol consumption was stratified into different categories (non-drinkers; low consumption (more than 0 but less than 2 alcoholic beverages per week); moderate consumption (2-14 alcoholic beverages per week); high consumption (more than 14 alcoholic beverages per week)) no dose-response relationship in the odds ratios related to the amount of alcohol consumption was found. For rheumatoid arthritis, odds ratios by amount of alcohol consumption relative to non-drinkers, were: low consumption: OR 0.12 (95%CI 0.08-0.18), moderate OR 0.46 (95%CI 0.36-0.59), and high OR 0.17 (95%CI 0.12-0.25). For the other forms of arthritis the analyses yielded similar results (data not shown).

Effect of symptom duration on alcohol consumption

To investigate if a long symptom duration of arthritis prior to presentation might result in decreased alcohol consumption, we evaluated whether there was an association between symptom duration and alcohol consumption. To this end, the symptom duration at first presentation was divided into three categories based on cumulative tertiles (short (0-2.0 months), medium (2.1-6.0 months), and long (>6.0 months)). For this analysis, patients with all different forms of arthritis were combined. There was no association between

sympton duration and the percentage of arthritis patients that reported drinking alcohol (short 62%, medium 53%, and long 60%)

Systemic inflammation and alcohol consumption

To examine if the inverse association between alcohol consumption and arthritis was related to the degree of inflammation, the presence of alcohol consumption was related to the level of systemic inflammation, as reflected by the level of the ESR (within the group of cases), and ESR was stratified into four groups. The level of the ESR was inversely correlated with alcohol consumption (p = <0.001) (Figure 1).

We also evaluated whether there was an association between a subjective marker for disease activity, in the form of the visual analogue scale on general health and the reporting of drinking alcohol. In contrast to our findings with regard to ESR, there was no association between the level of general health and reporting of drinking alcohol.

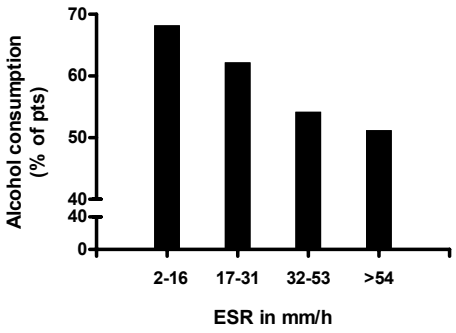

Figure 1: Alcohol consumption by ESR category.
Pearson test over all four categories <0.001
Comparison of ESR 2-16 vs ESR 17-31: p-value 0.090
ESR 2-16 vs ESR 32-53: p-value <0.001
ESR 2-16 vs ESR >54: p-value <0.001

Reported alcohol consumption in ACPA-positive RA patients compared to other forms of arthritis

A recent population based case-control study of two Scandinavian cohorts showed that alcohol consumption is associated with attenuation of the effect of established risk factors for RA; smoking and HLA-DRB1 shared epitope with regard to ACPA-positive RA [18].

To investigate whether reported alcohol consumption may be particularly negatively associated with the development of RA compared to other arthritides, a subgroup analysis was performed comparing the RA patients stratified for ACPA-status, with the patients with other forms of arthritis (n=273). This revealed a particularly negative association in

ACPA-positive RA patients (n=257) (OR 0.59, 95% CI: 0.36-0.99), compared to other forms of arthritis. Correction for the ESR-level slightly changed this risk (OR 0.63, 95% CI: 0.38-1.07). No differences were observed between alcohol consumption and the risk of ACPA-negative RA relative to the other forms of arthritis (data not shown).

Effect of alcohol consumption on radiographic progression and remission

To further investigate the negative association between the reported alcohol consumption and RA, we analyzed the effect of alcohol consumption on remission and radiographic progression. An increase in remission or decrease in radiographic progression would support the notion that alcohol might have an immunomodulatory effect in the process of inflammatory arthritis.

To compare the progression in radiographic destruction over 7 years, the rate of progression was plotted within the four alcohol consumption categories (none, low/little, moderate, high/substantial) (Figure 2). No significant association between alcohol consumption and rate of joint destruction over 7 years follow-up was found.

With regard to remission, there was no association between alcohol consumption and the frequency with which RA patients achieved remission (data not shown).

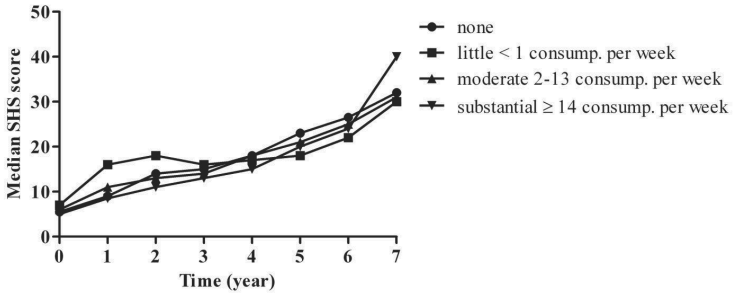

Figure 2: Median joint destruction over 7 years in RA patients in four alcohol categories.

DISCUSSION

This study shows that patients presenting with arthritis report less alcohol consumption than population controls, regardless of the type of arthritis. This may indicate a protective effect of alcohol on the development of arthritis, which is not specific for RA. Alternatively, it may be that patients stop drinking due to the presence of disease.

There was no dose-response relationship with the amount of alcohol consumed. Other studies reported varying dose-response relationships within categories with low or moder-

ate[25, 26] respectively high[18] alcohol consumption. Thus it is at present difficult to draw any definitive conclusions about a possible dose-effect of alcohol consumption on the risk of RA.

The inverse association between the ESR level and alcohol consumption shows that patients with more severe systemic inflammation report drinking less alcohol, or alternatively, that alcohol may protect against the development of more systemic inflammation. This last hypothesis is supported by reports that have shown a suppressive effect of alcohol on the level of systemic inflammation [27, 28]. Reports on alcohol use in other diseases with an inflammatory background have also shown a protective effect of alcohol consumption, which supports a more general role of alcohol in suppressing systemic inflammation [29, 30]. Thus, the association between alcohol consumption and arthritis might be due to a more general effect of alcohol on systemic inflammation rather than a specific protective effect in RA. It could be postulated that patients suffering from any illness tend to drink less due to compromised general health. We evaluated the visual analogue scale on general health, as a subjective marker for disease activity, in relationship to alcohol consumption. There was no correlation between the level of general health and reporting of drinking alcohol.

In the subgroup analysis investigating the association of ACPA with alcohol consumption, there was an inverse association, suggesting that alcohol consumption may be particularly negatively associated with ACPA-positive RA. In order to further analyze the effect of alcohol consumption specifically for ACPA-positive RA, we performed a combined analysis of our data and of previously published data from Sweden (the EIRA cohort) and Denmark (the COCORA cohort) comparing ACPA-positive to ACPA-negative patients. This small "meta"-analysis yielded an OR 0.31 (95% CI 0.23-0.40), with a consistent protective effect seen in all cohorts. The analysis of all available data showed that the effect of alcohol was consistent in both the Dutch, the Swedish and the Danish cohort when controls were used that suffered from arthritis but that do not harbour antibodies to citrullinated antigens. These data are very relevant because they provide evidence that in addition to smoking, alcohol consumption is a risk factor that differs between ACPA-positive and ACPA-negative RA. These data support the concept that ACPA-positive disease is a different disease than ACPA-negative disease [31].

Källberg et al showed a more pronounced risk reduction with alcohol consumption among carriers of HLA-DRB1 shared epitope alleles than among non-carriers [18]. In our study no association was found between the effect of alcohol consumption and the presence of the shared epitope within the ACPA-positive RA patients.

If there was to be a real immunomodulatory effect of alcohol this would have effect on long-term phenotype such as rate of joint destruction or ability to achieve remission. Nissen et al [26] previously showed a J-shape relation between alcohol consumption and radiological progression; low alcohol consumption was most beneficial compared to no- and heavy consumption. We repeated this analysis (with similar adjustment variables) in our study, but did not find a significant association between alcohol consumption and rate

of joint destruction over 7 years of follow up. Although this could be due to lack of power in our analyses, no tendency toward reduced radiographic progression was observed. In our study merely baseline data on alcohol consumption were used in analyses addressing this topic, due to the strict advice to stop drinking alcohol in combination with the use of some DMARDs, such as methotrexate, thereby causing bias. In the study performed by Nissen et al both baseline and follow-up data on alcohol consumption where used in the analyses and subsequently have influenced the data on radiographic progression.

It is unknown how long and in what way the immunomodulatory effect of alcohol will affect disease manifestation and the long-term disease course. Jonsson et al [12] showed that collagen induced arthritis remained non-destructive in mice that were provided with 10% ethanol in drinking water over a period of 6 weeks. The beneficial effects of ethanol might be mediated by up-regulation of testosterone production which in turn inhibits NF-κB activation leading to decreased cytokine/chemokine production (IL-6, MIP-1α, TNF-α) and decreased chemotactic activity of leukocytes.

In contrast to the inhibitory effects of acute alcohol, prolonged alcohol treatment in mice results in augmentation of macrophage TNF-α production [32], and in increased expression of co-stimulatory molecules CD80 and CD86 on TLR9-activated CD11b-positive splenocytes thereby contributing to systemic immunodysregulation including T-cell activation [33, 34]. Overall therefore, it is difficult to determine the immunomodulatory role of alcohol in the course of arthritis, based on the different outcomes of in vivo experiments in mice.

One of the main comments on our study could be that the effect seen is being caused by recall bias. This means that cases might not actually have been drinking less alcohol but reported to be drinking less when faced with a questionnaire in the outpatient clinic, while the drinking behaviour was in fact unchanged. The questions asked in cases and general population controls were similar therefore minimising a major effect of recall bias [35]. The assumption that drinking behaviour may be influenced by the disease duration was not confirmed by our data.

In summary, this study suggests that patients presenting with arthritis report less alcohol consumption, regardless of the form of arthritis. This observation could be due to the fact that compromised general health leads to decreased alcohol consumption. The inverse association between alcohol and ESR might be related to the effect of alcohol on systemic inflammation rather than a protective effect specific for RA although our data also suggest that alcohol consumption may be particularly protective against ACPA-positive RA.

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