Clinical Investigations

Type of Alcoholic Beverage and First Acute Myocardial Infarction: A Case-Control Study in a Mediterranean Country

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Summary

Background: Although international comparisons have consistently found an inverse association between wine and coronary heart disease, few epidemiologic studies are available in Southern Europe. We assessed the association of wine, red wine, and the pattern of drinking wine during meals with the risk of myocardial infarction.

Hypothesis: We specifically evaluated three hypotheses: (1) Is the protection against incidence of nonfatal myocardial infarction stronger for wine than for other alcoholic beverages? (2) Does the wine consumed during meals represent a more beneficial pattern of alcohol consumption? (3) Is red wine more advantageous than other types of wine?

Methods: A case-control study (171 cases, 171 matched controls) was conducted in Spain. Multiple dietary and nondietary potential confounders were assessed.

Results: Exposure to wine, red wine, and wine during meals was associated with risk reductions similar to those of other alcoholic beverages (point estimates of the odds ratio for low and high intake were 0.48 and 0.38 for wine; 0.42 and 0.55 for other beverages). However, after controlling for total alcohol intake, wine consumption (g/day) improved the prediction of a myocardial infarction.

Conclusions: Our data showed that red wine or drinking wine during meals was similar to alcohol from other sources

for reducing coronary risk. However, an additional benefit of wine, keeping constant overall alcohol intake, deserves further research.

Key words: Mediterranean diet, wine, myocardial infarction, case control

Introduction

A lower risk of coronary heart disease (CHD) has been consistently found among alcohol drinkers compared with abstainers.^{1–6} The risk reduction provided by ethanol intake is more likely to represent a causal association with an L-shaped pattern, that is, light drinkers have a reduction in risk but heavy drinkers do not achieve further reductions.⁷

International comparisons^{8–11} as well as ecological findings within Mediterranean countries¹² have suggested that wine may provide a greater protection against CHD than ethanol from beer or spirits. This hypothesis is supported by mechanistic findings related to polyphenols and other compounds contained in wine, and especially in red wine, that may exert inhibition of platelet aggregation,¹³ antioxidizing properties, and vasorelaxing and other beneficial effects on endothelial function.^{14–16} Genetic studies support these mechanisms.¹⁷ In spite of laboratory findings, most epidemiologic studies have failed to detect large differences in benefits between the various types of alcoholic beverages.^{18, 19} Some studies have reported a stronger protective effect for wine in their point estimates,^{20–24} but, in general, there were no statistically significant differences. In most of these studies the number of people consuming wine was negligible.^{18, 25}

A wide consensus supports that the alcoholic content of the different drinks and no other component is what appears to be linked to lower risk.^{4, 6, 18} A likely alternative explanation for the apparent stronger effect of wine in ecologic studies is that the greater variability in overall alcohol intake is precisely found in countries where wine is the predominant beverage.⁹ In this context, a recently published study conducted in a predominantly beer-drinking population did not find a protection for wine,²⁶ but it did for beer. Another plausible explanation for the inconsistencies among studies is that confounding has

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not been adequately controlled. A need for studies assessing lifestyle factors such as diet, which frequently correlate with the type of alcoholic drinks consumed, has been recently highlighted⁶ because wine drinkers are supposed to have an overall healthier diet and lifestyle than drinkers of other beverages.

An ancillary hypothesis that demands further evaluation is that the traditional Mediterranean pattern of wine consumption during meals may exert a favorable effect on CHD risk because it may improve postprandial hyperlipidemia.^{8,27}

Few epidemiologic studies to assess the relationship between individual wine intake and CHD risk have been carried out in Southern Europe, where a high level of wine drinking on a regular basis exists.^{22,28–31} Some of these studies have only used mortality,^{28,29} but have not assessed nonfatal CHD.

The present study assessed the potential reduction in the risk of incident acute myocardial infarction (AMI) that can be derived from the intake of different types of alcoholic beverages in a Mediterranean population with a high wine intake. We specifically evaluated three hypotheses: (1) Is the protection against incident nonfatal myocardial infarction stronger for wine than for other alcoholic beverages? (2) Does the wine consumed during meals represent a more beneficial pattern of alcohol consumption to lower CHD risk? (3) Is red wine more advantageous than other types of wine?

Material and Methods

Selection of Cases

A hospital-based case-control study was conducted in Navarre, Spain. Several potential limitations in the selection of cases, such as the possibility of reverse causation by including prevalent cases or the lack of specificity in the case definition, were avoided by including only definitive cases of AMI according to the criteria of the MONItoring trends and determinants in Cardiovascular disease (MONICA) project.³² We included all new cases admitted to one of the three third-level university hospitals of Pamplona (Spain) within the periods October 1999 to June 2000 or October 2000 to February 2001. A previous history of angina pectoris, CHD, or other prior diagnosis of major cardiovascular disease were considered exclusion criteria. We identified 180 eligible cases. Nine of these refused to participate (participation 95%). Most cases (97%) were assessed in the cardiology ward once they had been discharged from the coronary unit (average lag time: 7 days).

Selection of Controls

After a pilot study, we judged that population controls were not suitable because their participation would be very low and dependent on their alcohol consumption. Therefore, in order to ensure a high participation rate among controls and to avoid their biased selection, we selected hospital controls from the source population that gave rise to the cases. Controls were patients who would be treated in the same three hospitals as cases if they developed a myocardial infarction. We matched a

control subject of the same age (5-year bands), gender, and hospital to each case. Eligible controls were patients admitted to different wards of the same hospital during the same month that matched cases. We included controls with a variety of diagnoses to have the advantage of diluting the biasing effects of including a specific diagnostic group.³³ We excluded major groups of diseases known to be related to alcohol. However, some trauma patients and others with gallbladder disease were included as controls, and we performed sensitivity analyses to assess the possibility of selection bias (see below). Eight eligible controls refused to participate (participation 96%); they were replaced by other patients of similar characteristics for matching variables.

Exposure Assessment

We used a self-administered, semi-quantitative food-frequency questionnaire (136 items), previously validated in Spain,³⁴ to assess diet and alcohol consumption. We assessed alcohol intake during the previous year with six items (red wine, sweet wine, other kinds of wine, wine during meals, beer, and spirits), specifying the typical volume of each drink. There were nine options for frequency of consumption from “never” to “more than 6 drinks/day.” Emphasis was added to ensure that the answers were related to long-term (past year) and not to recent changes. A dietitian updated the nutrient data bank using the latest available information included in the food composition tables for Spain.

To quantify the volume and intensity of leisure-time physical activity, we computed an activity metabolic equivalent (MET) index by assigning a multiple of resting metabolic rate (MET score) to each of 19 activities, yielding an overall value of weekly MET-hours.^{35–37}

A physician clarified any questions the patient may have had in completing the questionnaire, ensured that there were no missing values for any item, and subsequently conducted a face-to-face interview with the patient assessing coronary risk factors (smoking, diabetes, high blood pressure, high blood cholesterol) and family history of coronary disease. Systolic and fifth-phase diastolic blood pressure readings were taken and weight and height were measured. We calculated the body mass index (BMI) as the weight in kilograms divided by the squared height in meters (kg/m^2).

Statistical Analysis

The association of consumption of alcohol and specific beverages with myocardial infarction was calculated through multivariable conditional logistic regression using matched data of 171 case-control pairs, introducing in first place nondietary confounders, and, in a second model, we added the dietary confounders. Reported *p* values were two-tailed; values <0.05 were considered significant.

We assessed the additional linear contribution of each alcoholic beverage to the protection conferred by alcohol using the likelihood ratio test to compare two conditional logistic models, a basic model with alcohol and all the confounders as in-

dependent terms, and alternative models with alcohol and all the confounders and the particular alcoholic beverage (g/day) as an independent continuous variable. We used the same procedure to evaluate the hypothesis that wine consumed during meals provides an additional benefit, adding wine during meals (yes/no) to a previous model in which alcohol and all potential confounders were already included.

We performed sensitivity analyses, repeating the conditional logistic regression modeling after excluding those control subjects with diagnoses potentially related to alcohol consumption.

Results

As expected, proportions of CHD risk factors (hypercholesterolemia, hypertension, smoking, diabetes) were higher among cases. We also found higher BMI and lower METS-hours/week among cases. The distribution of sociodemographic variables was similar in cases and controls (data not shown).

The average daily intake of ethanol was 18.4 g (12.3 g from wine, 3.3 g from beer, and 2.8 g from spirits).

Table I shows the distribution of potential confounding variables across categories of alcohol or beverage consumption among control subjects. Women and older subjects were more likely to be abstainers; therefore, we present all comparisons in Table I adjusted for age and gender (see footnote in Table I). A

higher socioeconomic status was associated with higher alcohol intake and higher consumption of every type of beverage, although this was more evident for educational level than for occupation. With the exception of hypertension, the presence of other strong risk factors for CHD (smoking, hypercholesterolemia, diabetes, and positive family history of CHD) was greater among drinkers of alcohol or heavier wine consumers. Aspirin intake was lower among controls with higher alcohol consumption either from wine or from other sources. A higher BMI was found among those with a higher consumption of wine. Energy intake and energy expenditure were greater among drinkers of every kind of alcoholic beverage. The best overall dietary profile was found among controls whose wine consumption was > 10 g/day.

Table II shows that overall alcohol consumption was inversely associated with the risk of myocardial infarction. The relative risk reduction was less apparent in the matched analysis adjusting for age, gender, hospital, and total energy intake than after additional adjustment for other confounders. The lower risk was found for those participants consuming 10 to 20 g/day of alcohol, but the findings for total ethanol are compatible with an L-shaped pattern. Additional adjustment for the main dietary factors did not substantially modify the estimates. A similar procedure was used with wine consumption and with alcohol from other sources. The point estimates of the adjusted odds ratios (OR) for each level of consumption were

TABLE I Distribution of potential confounding variables across categories of alcohol and alcoholic beverage consumption among control subjects (n=171)

	Total alcohol intake		Wine intake		Alcohol from other beverages (not wine)	
	Abstainers	>10 g/day	<10 g/day	>10 g/day	<10 g/day	>10 g/day
Ethanol intake (g/day, mean)	0	36.7	3.1	25.6	7.3	29.0
Age (mean)	65.1	59.5	61.1	65.3	61.7	58.4
Men	53	96	67	88	65	97
White collar ^a (%)	15	18	20	30	19	20
Educational level higher than primary ^a (%)	6	58	19	32	19	28
Married ^a (%)	56	70	65	79	71	77
Current smokers ^a (%)	6	33	11	26	17	23
High blood cholesterol ^a (%)	26	62	22	33	24	34
High blood pressure ^a (%)	38	18	30	29	40	21
Diabetes ^a (%)	9	13	6	8	6	8
Aspirin intake ^a (%)	18	4	11	7	12	2
Family history of CHD <60 years ^a	0	8	0	6	2	6
Body mass index (kg/m ² , mean) ^b	26.9	26.9	26.7	27.4	27.3	27.4
Leisure-time phys. activity (METS-h/week, mean) ^b	27.8	35.6	29.4	34.3	29.6	35.4
Total energy intake (kcal/day, mean) ^b	2315	2650	2359	2649	2434	2634
Total fat intake (mean) %E ^b	30.9	29.2	31.4	31.0	31.7	30.1
MUFA/SFA intake (mean) ^b	1.43	1.50	1.51	1.55	1.50	1.56
Glycemic load (g/day, mean) ^b	221	221	223	225	217	227
Total fiber intake (g/day, mean) ^b	33.2	30.0	31.3	32.2	32.2	31.0
Folic acid intake (microg/day, mean) ^b	435	407	420	442	435	426
Olive oil intake (mg/day, mean) ^b	18.5	26.3	21.8	27.1	22.3	27.6

^a Adjusted for age and gender (logistic regression modeling).

^b Adjusted for age and gender (linear regression modeling).

Abbreviations: CHD = coronary heart disease, MUFA = monounsaturated fatty acids, SFA = saturated fatty acids.

TABLE II Odds ratios (95% confidence intervals) of a first myocardial infarction according to the consumption of alcohol or specific alcoholic beverages

	Total alcohol intake (g/day)					Alcohol from wine (g/day)			Alcohol from other sources (g/day)		
	0	<10	10–19.9	20–29.9	≥30	0	0.1–10	≥10	0	0.1–10	10–19.9
Controls/cases	34/42	60/50	18/11	23/28	36/40	48/55	67/56	56/60	71/77	73/64	27/30
Matched OR (gender, age, hospital, total energy)	1 (ref.)	0.63 (0.34–1.18)	0.44 (0.17–1.17)	0.88 (0.38–2.00)	0.87 (0.38–1.98)	1 (ref.)	0.71 (0.41–1.21)	0.90 (0.48–1.71)	1 (ref.)	0.76 (0.44–1.30)	0.93 (0.47–1.85)
Multivariate adjusted OR ^a	1 (ref.)	0.38 (0.15–0.92)	0.20 (0.05–0.79)	0.43 (0.13–1.36)	0.40 (0.13–1.27)	1 (ref.)	0.47 (0.22–0.97)	0.49 (0.20–1.22)	1 (ref.)	0.43 (0.20–0.91)	0.55 (0.21–1.44)
Multivariate adjusted OR ^b	1 (ref.)	0.38 (0.15–0.97)	0.24 (0.06–1.02)	0.41 (0.12–1.34)	0.30 (0.09–1.02)	1 (ref.)	0.48 (0.23–1.02)	0.38 (0.15–1.00)	1 (ref.)	0.42 (0.20–0.91)	0.55 (0.21–1.44)
Multivariate adjusted OR	No	Yes					No	Yes	No	Yes	
	1 (ref.)	0.35 (0.14–0.85)					1 (ref.)	0.45 (0.22–0.93)	1 (ref.)	0.46 (0.22–0.94)	

^a Conditional logistic regression (age-, hospital-, and gender-matched pairs), adjusted for total energy intake, smoking, body mass index, high blood pressure, high blood cholesterol, diabetes, leisure-time physical activity (METs-hours/week), aspirin use, family history of coronary heart disease, marital status, occupation, and study level.

^b Additionally adjusted for olive oil consumption, ratio of monounsaturated to saturated fat, folic acid, and total fiber intake.

Abbreviations: OR = odds ratio, METS = metabolic equivalent.

very similar for wine and for other alcoholic beverages. A slightly lower OR (0.38, $p = 0.05$) was found in the highest category (> 10 g/day) of wine consumption than in the same category of alcohol intake from non-wine sources (0.55, $p = 0.22$), suggesting that the benefit of wine may be also important at higher intakes. When we dichotomized the exposure variables, we found a stronger protective effect for overall alcohol than for particular beverages (wine or non-wine sources), as it is shown in the last column of Table II. The fully adjusted ORs with dichotomized exposures were 0.45 (95% confidence interval [CI] 0.22–0.93) for wine, 0.37 (0.19–0.75) for beer, and 0.75 (0.38–1.48) for spirits.

When we excluded control subjects who were admitted to the hospital for cancer (24 controls), trauma ($n = 35$), or gall-bladder disease ($n = 9$), and their matched cases, and when we repeated all the previous analyses, the point estimates for the OR were very similar, although the CIs were wider. The respective ORs were 0.24 (95% CI 0.06–0.96; $p = 0.04$) for total alcohol consumption, 0.33 (0.10–1.06; $p = 0.06$) for wine, and 0.47 (0.18–1.20; $p = 0.11$) for alcohol from other sources.

When we assessed the consumption of red wine or the pattern of wine drinking during meals as exposures (Table III), the point estimates for the ORs were < 1.00 for all categories, but they were in a similar range as those for overall alcohol intake or for alcohol from non-wine sources. Our findings were also compatible with an L-shaped pattern for these two exposures.

We also fitted a conditional logistic regression model, using alcohol as the exposure variable with the five categories shown in Table II and controlling for dietary and nondietary confounders. To this basic model we added, one by one, each of the alcoholic beverages as continuous variables (g/day) and the pattern of drinking wine during meals. The likelihood ratio test comparing these models showed a statistically significant result ($p = 0.037$) only for wine, but not for alcohol from other sources. On the other hand, regarding red wine or the pattern of wine drinking during meals, we found no further reductions in risk (Table IV).

Discussion

This is the first case-control study of diet and myocardial infarction conducted in Spain. Our results are consistent with a previous case-control study in France,²² showing similar relative risks for each type of alcoholic beverage. However, we found that wine intake (as a continuous variable) significantly improved prediction of the probability of CHD provided by overall alcohol intake, suggesting an additional benefit. This pattern is consistent with the reduction associated with the highest level of wine consumption in two previous Mediterranean case-control studies.^{30, 31} Our findings suggest that a monotonic risk reduction is associated with progressively higher intake of wine, keeping constant the overall alcohol intake. The protection from wine would be more consistent with an inverse linear trend than with an L-shaped curve. Nevertheless, the statistical significance for this test was only marginal, and further corroboration is needed.

TABLE III Odds ratios (95% confidence intervals) of a first myocardial infarction according to the consumption of red wine and the consumption of wine during meals

	Red wine (drinks/day)				Drinks of wine during meals			
	0	>0 and <1/day	1/day	>1/day	0	>0 and <1	1	>1
Controls/cases	57/67	41/30	25/24	48/50	64/75	31/23	29/25	45/48
Matched OR (gender, age, hospital, total energy)	1	0.59	0.78	0.83	1	0.64	0.70	0.91
	(ref.)	(0.32–1.09)	(0.42–1.48)	(0.44–1.54)	(ref.)	(0.33–1.21)	(0.37–1.32)	(0.48–1.74)
Multivariate adjusted OR ^a	1	0.38	0.79	0.59	1	0.33	0.55	0.42
	(ref.)	(0.16–0.89)	(0.34–1.85)	(0.25–1.40)	(ref.)	(0.12–0.91)	(0.23–1.34)	(0.15–1.15)
Multivariate adjusted OR ^b	1	0.39	0.79	0.48	1	0.29	0.57	0.51
	(ref.)	(0.16–0.95)	(0.34–1.85)	(0.19–1.20)	(ref.)	(0.11–0.79)	(0.24–1.37)	(0.19–1.34)

^a Conditional logistic regression (age-, hospital-, and gender-matched pairs), adjusted for total energy intake, smoking, body mass index, high blood pressure, high blood cholesterol, diabetes, leisure-time physical activity (METs-hours/week), aspirin use, family history of coronary heart disease, marital status, occupation, and study level.

^b Additionally adjusted for olive oil consumption, ratio of monounsaturated to saturated fat, folic acid, and total fiber intake.

Abbreviation as in Table II.

TABLE IV Improvements in conditional logistic models relating alcohol with coronary heart disease, adding other terms for total wine, red wine, pattern of drinking wine during meals, and other alcoholic beverages (not wine)

Model	Odds ratio (exposure)	Improvement in the model (likelihood ratio test)
Alcohol (5 categories), total energy intake, ^a smoking (4 categories), body mass index, ^a high blood pressure, high blood cholesterol, diabetes, leisure-time physical activity (METs-hours/week), ^a aspirin use, family history of coronary heart disease, marital status, occupation, study level (4 categories), olive oil, ^a monounsaturated to saturated fat ratio, ^a folic acid, ^a total fiber intake ^a	(Basic model) (See Table II)	(Basic model)
Adding spirits ^a (g/day) to the basic model	0.64 (+10 g/day)	p = 0.591
Adding beer ^a (g/day) to the basic model	1.01 (+10 g/day)	p = 0.946
Adding wine ^a (g/day) to the basic model	0.69 (+10 g/day)	p = 0.037
Adding red wine ^a (g/day) to the basic model	0.81 (+10 g/day)	p = 0.162
Adding pattern of drinking wine during meals (yes/no) to the basic model	0.52 (pattern)	p = 0.227

^a Classified as a continuous variable. All other variables are dichotomous if not otherwise indicated.

Abbreviation as in Table II.

The number of patients with CHD exposed to wine consumption in previous studies has been small. If wine were the main alcoholic beverage responsible for lower CHD rates in Mediterranean countries, the ideal setting to evaluate its role would be a Mediterranean country; however, no results from a large Mediterranean cohort are available to date, with the exception of those using only mortality data.^{28,29} In our study, 21% of participants (36 cases/37 controls) consumed only wine, and we add evidence to evaluate this hypothesis.

The two advantages of our study were that (1) we used non-fatal myocardial infarction as the outcome, because fatal and mixed outcomes have lower specificity; and (2) ethanol intake was categorized in detail to allow for better assessment of the shape of the dose-response curve.⁷

A small subset of the participants from our control group were hospitalized patients with cancer, trauma, or gallbladder disease, which may be related to ethanol intake.³⁷ However, we used this subset to perform sensitivity analysis and we found no evidence of a selection bias due to the inclusion of these patients as controls.

In any case-control study, fatal cases may be lost for the case series if they are fatal early; however, an inverse association of alcohol with coronary death has been consistently reported in cohort studies.⁷ Accordingly, patients not selected for our study because of early death would be less likely to be alcohol drinkers and the bias would tend toward null.

A proportion of myocardial infarctions are silent, and it is possible that cases exposed to alcohol may be more likely to be silent, but this proportion is not likely to be high³⁸ so as to cause bias.

A major concern in many case-control studies of diet and chronic disease is recall bias; however, recall of alcoholic beverages is not as problematic as recall of other exposures.¹⁸ In the validation of the food frequency questionnaire,³⁴ the highest correlation coefficients were found precisely for alcohol intake ($r = 0.90$). Interviewing physicians were not blinded to the case-control status of patients, but they did not directly collect data on alcohol from patients. Patients answered the questionnaire themselves, and therefore interviewer bias is not likely to have happened.

International comparisons and ecological studies have suggested that wine consumption is inversely associated with mortality rates for CHD also in Spain.¹² Although these designs are specially prone to flaws, they can mainly represent that wine is the main source of ethanol in the Mediterranean diet.

Conclusion

Our findings are consistent with the potential role of wine consumption as one of the beneficial elements of a Mediterranean-style diet,^{39,40} but further corroboration is still needed and may come from large follow-up studies conducted in Mediterranean populations.

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