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Alcohol Consumption and Health

Alkoholkonsum und Gesundheit

Zusammenfassung

In dieser Übersicht wird die epidemiologische Evidenz der Beziehung zwischen dosisabhängigem Alkoholkonsum und dessen klinischen Folgen dargelegt, inklusive allgemeine Mortalität. Es werden die wichtigen Mechanismen dargelegt, welche den protektiven Effekt einer moderaten Alkoholkonsumption bezüglich kardiovaskulärer Erkrankungen stützen. In zahlreichen epidemiologischen Studien hat sich eine gegenläufige Beziehung zwischen moderatem Alkoholkonsum und kardiovaskulärer Erkranung herausgestellt. Darüberhinaus konnte gezeigt werden, dass die Häufigkeit auch einer Reihe anderer Krankheiten bei moderaten Trinkern gegenüber abstinenten Personen vermindert ist, während exzessives Trinken in allen Fällen schädlich ist. Vorläufig bleibt die Frage offen, ob nicht auch geringe Dosen von Alkohol dessen schädliche Effekte zu kompensieren vermögen. Als mögliche Mechanismen, auf denen der kardioprotektive Effekt beruhen kann, werden die Wirkungen des Alkohols auf Lipide, Plättchenaggregation, Fibrinogen, Tissue-Plasminogen-Aktivator (TPA), TPA-Inhibitor und Omega3-Fettsäuren diskutiert. Insbesondere für Wein kommen noch zusätzliche Mechanismen zur kardiovaskulären Protektion in Frage.

Schlüsselwörter: Alkohol, Wein, Vaskuläres Risiko,Gesamtmortalität, Metaanalyse

Abstract

The aim of this review is to discuss the epidemiological evidence of the relationship between alcohol dosing and clinical out-comes – including all-cause mortality – and the major mechanisms supporting the protective effect of moderate intake of alcohol against cardiovascular disease. An inverse association between moderate alcohol intake and cardiovascular risk has been observed in many epidemiological studies. In addition, several other diseases also occur less frequently in moderate drinkers than in non drinkers, whereas excess of drinking is always harmful. The question remains whether at low dosage too the benefit of alcohol overcomes its harmful effects. Among the mechanisms related to the potential cardio-protective benefits, effects of alcohol on lipids, platelet aggregation, fibrinogen, tissue–Plasminogen Activator, plasminogen activator inhibitor and omega-3 fatty acids will be discussed. Wine possibly acts through mechanisms that might provide additional cardiovascular benefits.

Keywords: Alcohol, Wine, Vascular Risk, Total Mortality, Meta-analysis

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Introduction

Studies on alcohol and its harmful or beneficial effects on human health have a long history, starting from anecdotal accounts in biblical times to more recent rigorous studies of populations.

An inverse association between moderate alcohol consumption and cardiovascular disease (CVD) has been repeatedly observed in epidemiological studies.[1] In addition, other diseases are also known to occur less frequently in moderate drinkers than in non drinkers,[2] whereas excess of drinking is unquestionably harmful.[3] The question has been raised whether at low dosage the benefit of alcohol could overcome its harmful effects.[4] The relationship between alcohol and mortality has been represented as a J-shaped curve attributed to a combination of beneficial and harmful effects.[5] Indeed, if low alcohol intake is inversely related to CVD, an increased risk of certain cancers, cirrhosis and death from accidents or violence is associated with increasing alcohol consumption.[6]

Since wine intake was suggested to be the explanation for the lower than expected CVD mortality rates in France,[7] many studies have dealt with the question whether wine might offer a greater protection in respect to other alcoholic beverages, most likely related to its non-alcoholic components.[8]

Epidemiological Evidence

Protection by alcohol and wine against CVD

In spite of a large number of experimental studies supporting this hypothesis, epidemiological evidence of a greater effect of wine has not been definitely established. A meta-analysis from our group[9] tested such a hypothesis. The overall protective effect against vascular disease was 32% (95%CI: 23% to 41%; 13 studies, 209 418 subjects) in favour of moderate (1 – 2 drinks a day) wine drinkers *versus* abstainers and somewhat inferior (22%, 95%CI: 14% to 30%; 15 studies, 208,036 persons) in favour of moderate beer drinkers *versus* abstainers. In addition, there was strong evidence from 10 studies (involving 176,042 persons) to support a J-shaped relationship between different amounts of wine intake and vascular risk (a statistically significant inverse association was found up to a daily intake of 150 ml of wine), whereas no significant relationship between different amounts of beer intake and vascular risk could be found.

Whether wine is better than beer or spirits remains therefore to be definitely established. Future studies addressing this issue should be of large sample size and carefully designed, because differences between beverages, if any, are expected to be limited and might reflect differences in the risk factor patterns among categories of drinkers rather than a true difference in CVD risk.

Protection against total mortality: alcohol is always dangerous or is there a window for net benefit?

If low alcohol intake is inversely related to CVD, the other side of the coin shows an increased risk of certain cancers, cirrhosis and death from accidents associated with increasing alcohol consumption.[10] As a consequence, strong concern exists on the possibility that at any dosage the benefit of alcohol could overcome its harmful effects.[11] To test such a hypothesis, we performed a meta-analysis including 34 prospective studies on alcohol and mortality.[12] We pooled findings from more than one million subjects and about 95,000 deaths from any cause. The J-shaped relationship between total mortality and increasing amounts of alcohol consumed, showed that low to moderate consumption of alcohol (≤ 1 drink/day in women and ≤ 2 drinks/day in men) significantly reduces total mortality, while higher doses increase it.

Are the beneficial effects of alcohol due to factors other than alcohol itself?

We paid special attention to the possible effect of confounding. Twenty-nine studies showed adjusted relative risks at least for age; among them, 15 were adjusted for social status too, and 6 for social status and dietary markers. Figure 1 shows relative

risks of total mortality for different levels of adjustment. P for difference was highly significant (P < 0.0001), showing that part of heterogeneity is attributable to adjustment. However, while the protection decreased in adjusted studies (the maximum protection fell from 36% to 17%), it remained substantial and statistically significant. Moreover, as the observed difference between the five not adjusted and the 29 adjusted studies could not be only due to the level of adjustment -these results coming from different studies- we compared adjusted or not unadjusted data from the same studies. In this case the effect due to known confounders (age, smoking, social status, dietary factors) led to the reduction of the maximum protection from 19% to 16%; for analogy, even in the pessimistic hypothesis that residual confounding would have a similar strength as the known one in lowering the protection, one can assume that the "real" (maximum) protection against total mortality associated with low consumption of alcohol would be largely higher than 10%. Although the protection by alcohol or wine decreases when data are adjusted, thus confirming the importance of confounding in assessing drinking effects, it remains in a range of undoubted public health value.[13]

The critical problem of inclusion of former drinkers in the control groups

We also investigated the degree to which the inclusion of former drinkers in control group influence the results.[14]

The inclusion in the control group of people who had stopped drinking owing to illness may have been overestimated protection of drinking in moderation. We tested this hypothesis by comparing studies that used as referent group the category of no alcohol intake and/or excluded former drink-

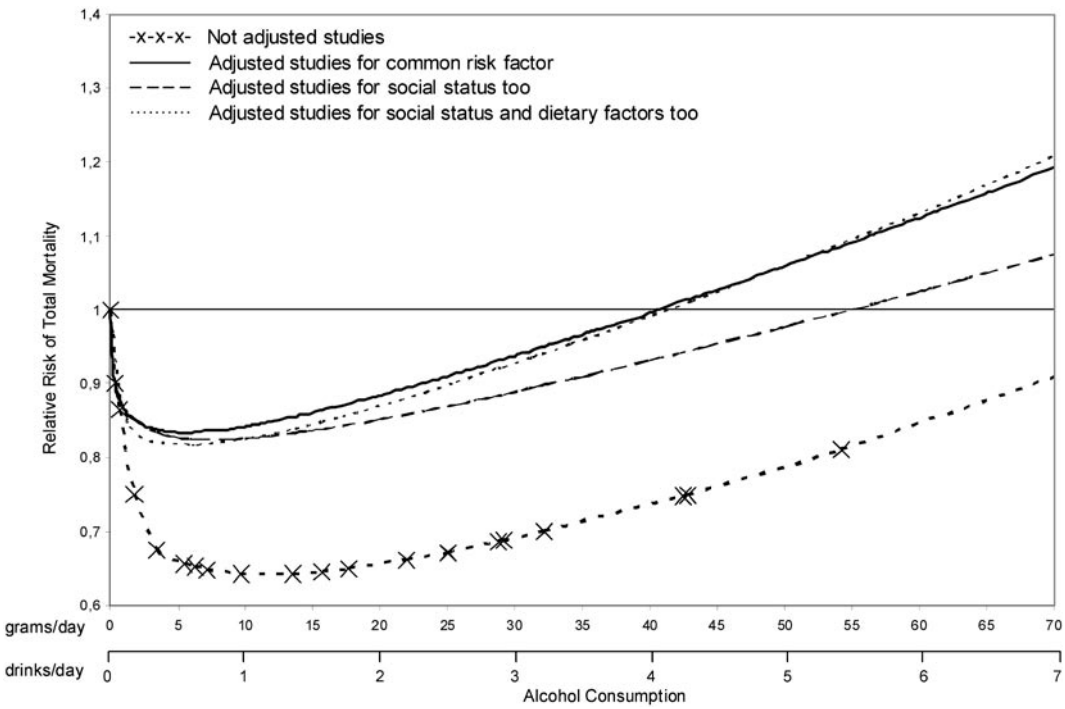

Fig. 1: Relative Risks of total mortality and alcohol consumption, according to the level of adjustment in the reviewed studies (adapted from Di Castelnuovo A., Costanzo S., Bagnardi V. et al.[2]).

ers with studies which, in contrast, included in the reference group occasional or former drinkers or people reporting low alcohol intake: the protection was indeed lower in the first studies, but remained statistically significant.

Are men and women similarly susceptible to protection or harm by alcohol?

Confronting dose-response curves separately in men and women we observed that the protection was apparent up to 3 drinks/day in men but only up to 2 drinks/day in women, whereas the maximum risk reduction was similar in men (17%; 99%CI: 15% – 19%) and females (18%; 99%CI: 13% – 22%). We concluded that the pooled curves for men and women were different for the range at which alcohol remains protective – in fact the inverse association in women apparently disappears at doses lower than in men – but comparable regarding the maximum protection.

Are alcohol benefits equally apparent in different world regions?

In females, pooled curves obtained using data from USA or Europe or other countries (Australia, Japan and China) were comparable. In contrast, strong differences were observed in males (P for difference was highly significant for each pairwise comparison), showing that part of heterogeneity in males is attributable to the set of the study. In particular, maximum risk reduction was in the range 20% – 28% in European but 14% – 19% in USA studies, and the protection extended up to 6 drinks/day in European but only up to 3 drinks/day in USA studies. Further sub-grouping of USA data according to ethnicity provided no evidence of heterogeneity.[15]

Mechanisms of action of alcohol

Alcohol affects several vascular and biochemical factors with potential cardio-protective benefits. Induced changes in lipid profile are thought to represent a major mechanism to reduce the risk for CVD-related mortality.[16]

However, other changes in vascular, haemostatic, and endothelial cell function may be important in contributing to reduce this risk, including decrease in platelet aggregation via inhibition of prostaglandin synthesis; by affecting fibrinogen, platelet aggregation, tissue-Plasminogen Activator (t-PA), and plasminogen activator inhibitor-1 (PAI-1). A positive association between moderate alcohol intake and endogenous t-PA antigen, a positive dose–response relationship between total alcohol consumption and t-PA and an inverse dose–response relationship between alcohol and fibrinogen were also observed. Alcohol inhibited development of atherosclerotic lesions in a dose-dependent fashion in mice and impeded early atherosclerosis in a dose-dependent manner. Moderate alcohol consumption was independently associated with reduced coronary atherosclerosis in humans.[17]

Increase of high-density lipoprotein levels

Concentration of plasma high-density lipoprotein (HDL) and its subfractions HDL3 mass decreased in temporary abstainers but not in moderate alcohol drinkers.[18] When the abstainers group re-started to drink, increased levels in HDL cholesterol and HDL3 mass but no change in HDL2 mass were observed. In stratified and multivariate regression analyses,[19] HDL cholesterol levels increased with increased frequency of consumption of beer, wine and spirits in a representative sample of the US adult population of whites and blacks of both sexes. After adjustment for common factors, there were higher age-adjusted HDL cholesterol levels with increasing reported quantities of alcohol consumed. In a study including about 5,000 Spanish men and women aged 25 – 74 years, total alcohol intake was significantly associated to increased HDL cholesterol in both sexes.[20]

Antithrombotic properties

An explanation for the "French paradox"[21] already mentioned, involved inhibition of platelet aggregation by alcohol, at consumption levels asso-

ciated with reduced risk of coronary heart disease (CHD). Alcohol would act through inhibition of prostaglandin synthesis, like aspirin. Subsequent studies have shown that several polyphenols, mainly contained in red wine, rather than alcohol, are able to inhibit platelet arachidonic acid metabolism and biosynthesis of thromboxane A2, a potent platelet aggregation inducer and a vasoconstrictor.[22]

Moderate alcohol consumption may affect fibrinogen concentration, t-PA, and PAI-1,[23] while a positive association between moderate alcohol intake and plasma concentration of endogenous t-PA was independent of HDL cholesterol levels.[24]

In a study conducted on more than 3,000 men aged 60 – 79 years without history of acute myocardial infarction, stroke or diabetes, a positive dose-response relationship was observed between total alcohol consumption and t-PA antigen and an inverse dose-response relationship between alcohol intake and plasma fibrinogen levels.[25]

Antiatherogenic properties

Antiatherogenic properties of alcohol were described in both animal and human studies. In a study on 1,676 men and 465 women undergoing coronary angiography,[26] multivariate analyses showed that alcohol consumption was associated with lower percent of lumen narrowing in the main coronary vessels, suggesting that moderate alcohol consumption is independently associated with reduced coronary atherosclerosis.

Alcohol consumption and omega-3 polyunsaturated fatty acids

More recently de Lorgeril et al have proposed an original mechanism to explain -at least in part- the protective effect of alcohol: the "fish-like effect of moderate wine drinking" hypothesis.[27]

Omega-3 fatty acids (ω3 FA) consumption reduces risk of sudden cardiac death in humans[28] and induces myocardial protection in animal experiments.[29] The Lyon Diet Heart Study (a cross-sectional study on French patients with CHD), showed that moderate wine consumption was associated with higher levels of "marine" ω3 FA in plasma[30] independently from the dietary intake of specific plant and marine ω3. The protection resulting from moderate alcohol drinking was suggested to be mediated by increased ω3 FA. These results were confirmed in a recent experimental study by the same research group.[31] They showed in rats that moderate alcohol consumption was associated with increased levels of ω3 FA both in plasma and in red blood cell membranes. The association of alcohol consumption with ω3 FA in both plasma and red blood cells was also lately studied in women and men enrolled in Italy, Belgium and England, in the framework of the IMMIDIET study[32]. Eicosapentanoic acid (EPA), docosahexanoic acid (DHA) and EPA+DHA in plasma, and EPA and EPA+DHA in red blood cells were all positively associated with alcohol intake. The association was stronger in women than in men. In the whole population the association between different beverages (wine or beer) and levels of ω3 FA in wine drinkers, the association was confirmed in wine drinkers both in plasma and red cell, while in beer and spirits drinkers only a weak association with DHA in plasma could be found.[33]

Additional mechanisms of action of wine

Wine (particularly red wine) possibly acts through additional mechanisms that might provide further cardiovascular benefits in respect to ethanol alone. Red wine contains many substances such as phenols and tannins, which influence low-density lipoprotein oxidation, platelet aggregation, endothelial function and smooth muscle cell proliferation.[34] It also contains a wide variety of polyphenols, including phenolic acids, stilbenes (resveratrol), and flavonoids (catechin, epicatechin and quercetin).[35] Some of these molecules inhibit lipoprotein oxidation, promote nitric oxide formation by vascular endothelium, inhibit thromboxane A2 biosynthesis in platelets and leukotriene biosynthesis in neutrophils, and regulate lipoprotein production and secretion. These actions occur through the in-

hibition of various enzymes such as phospholipase A2, cyclo-oxygenase 1 and 2, phosphodiesterase, and several protein kinases involved in cell signaling.

Antioxidant properties

Atherosclerotic plaque formation reportedly involves lipoprotein oxidation inside arterial walls. Resveratrol attenuated indeed oxLDL-induced cytotoxicity, apoptotic features, generation of reactive oxygen species and intracellular calcium accumulation.[36]

A small group of patients with acute coronary syndrome undergoing percutaneous coronary interventions was randomized either to consume red wine (250 ml daily) or to abstain from any alcoholic beverage. While the endothelium-dependent/independent dilation ratio significantly improved, after 2 months, in both groups, wine drinking only showed benefits on parameters of oxidative stress.[37]

The effects of moderate red wine consumption on antioxidant status were also investigated in a randomized controlled study on healthy volunteers.[38] Total plasma phenolic concentrations increased significantly after two weeks of daily moderate red wine consumption. The maximal concentrations of conjugated dienes and thiobarbituric acid-reactive substances in Cu-oxidized LDL were reduced but HDL cholesterol concentrations increased after red wine consumption.

Antithrombotic properties

Drugs that attenuate platelet aggregation, such as aspirin, are protective for ischemic heart disease.[39] Although alcohol by itself inhibits platelet aggregation or potentiates platelet inhibitory drugs,[40] red wine inhibits human platelet aggregation, mainly due to its polyphenolic compounds, resveratrol and quercetin being the most extensively investigated.[41] Aggregation of human platelets and the biosynthesis of thromboxane A2 are strongly inhibited by red wine,[42] while quercetin potentiates the inhibitory prostaglandin I2 by increasing levels of cyclic *adenosine* monophosphate. In human volunteers, moderate red wine consumption for few weeks decreased platelet aggregation[43] and plasma thromboxane B2 concentration.[44] As the mechanism of platelet inhibition by red wine might be different from that of other platelet-inhibiting substances, the effect of its moderate consumption in the prevention of coronary artery disease might be additive to that of aspirin or other drugs. In this context, Rotondo et al.[45] showed that trans-resveratrol and aspirin in combination inhibited *in vitro* human platelet aggregation more effectively than either compound used alone. Trans-resveratrol also prevented polymorphonuclear leukocyte (PMN) aggregation and formation of mixed conjugates between PMN and platelets. Trans-resveratrol appears thus to interfere with the release of inflammatory mediators by activated PMN and down-regulates adhesion-dependent thrombogenic PMN function, providing further biological plausibility to the protective effect of red wine consumption against CVD.

Tissue Factor (TF) is a lipoprotein that initiates the activation of blood coagulation cascade both *in vitro* and *in vivo*. The expression of TF by endothelial and mononuclear cells from healthy donors, challenged in vitro by different stimuli, was inhibited in a dose-dependent fashion by resveratrol or quercetin.[46] Both polyphenols also strongly reduced TF mRNA in both cell types, by reducing nuclear binding activity of the transacting factor c-Rel/p65, which was induced by the agonists. The diminished c-Rel/p65 activity was dependent in turn upon inhibition of degradation of the c-Rel/p65 inhibitory protein IkappaBalpha. These findings provide an additional molecular basis to explain the protective activity of red wine against cardiovascular disease where blood coagulation is activated and the resulting fibrin is deposited at vascular level.

Polyphenol interaction among themselves and with drugs

At variance with resveratrol and quercetin, little is known of the platelet effect of gallic acid, a polyphenol structurally similar to salicylic acid, the ma-

jor aspirin metabolite. In *vitro* experiments, all these three polyphenols shared a similar platelet antioxidant activity, although resveratrol and quercetin, but not gallic acid inhibited platelet aggregation and platelet thromboxane A2 biosynthesis.[47] In interaction experiments, gallic acid, similarly to salicylic acid, blunted the inhibition of platelet function induced by aspirin or by the other two polyphenols. The latter, in contrast, potentiated the anti-platelet effect of low concentrations of aspirin. Molecular modelling studies suggested that all three polyphenols – like salicylate – formed stable complexes into the cyclooxygenase-1 enzyme channel, with slightly different interaction geometries, compatible with the functional results mentioned above. The observed polyphenol-aspirin and polyphenol-polyphenol interactions at the platelet level, might be relevant to the healthy value of dietary polyphenols and to the observed variable response of both healthy individuals and patients to aspirin treatment (a phenomenon referred to as "aspirin resistance").

Anti-inflammatory properties

An association between alcohol consumption and concentrations of C-reactive protein (hs-CRP) and leukocyte count was reported by a German study[48][57] in 781 men and 995 women aged 18 – 88 years**.** Among men, alcohol consumption showed a U-shaped association with mean values of CRP and leukocyte count even after adjustment for age, smoking, body-mass index, HDL and LDL cholesterol, history of hypertension, education and income. In women, the associations were less strong. Non-drinkers and heavy drinkers had higher CRP concentrations than moderate drinkers, suggesting an anti-inflammatory action of moderate alcohol consumption.

Estruch et al.[49] performed a randomized, crossover, single-blinded trial to evaluate the effects of wine and gin on inflammatory biomarkers of atherosclerosis. Forty healthy Spanish men (mean age, 37.6 years) consumed 30 g ethanol per day as either wine or gin (virtually free of polyphenols) for 28 days. After either alcoholic beverage consumption, plasma fibrinogen and cytokine IL-1alpha were significantly decreased. The expression of cell inflammatory markers such as LFA-1, Mac-1, VLA-4 and MCP-1 decreased significantly after wine, but not after gin. Wine also reduced the serum concentrations of hs-CRP, VCAM-1 and ICAM-1. Although both alcoholic beverages showed anti-inflammatory effects, wine had the additional effect of decreasing hs-CRP, as well as monocyte and endothelial adhesion molecules. In the same group of volunteers, Badia et al.[50] found that TNF-alpha-induced adhesion of monocytes to endothelial cells was almost completely abolished after red wine consumption but was only partially reduced after gin consumption, supporting the anti-inflammatory properties of alcohol but more particularly of red wine.

Antiatherogenic properties

In a study on apolipoprotein E-deficient mice,[51] smaller atherosclerotic lesion areas and reduced susceptibility to oxidation of LDL were observed after either red wine or polyphenol chronic consumption, as compared with placebo. The susceptibility of LDL to aggregation was also reduced.

In an in vivo study on hypercholesterolemic rabbits, de-alcoholized red wine suppressed atherosclerosis without affecting plasma lipid levels,[52] a finding similar to that reported in hypercholesterolemic rats.[53] Human studies too suggest that the consumption of red wine[54] or alcohol-free red wine[55] leads to a significant increase in serum antioxidant activity and in the susceptibility of LDL to oxidation in vivo, limiting the extent of atheroma formation.[56]

It is worth mentioning here that, to date, the results of large randomized clinical trials assessing the use of antioxidant therapies (mainly vitamin E, rather than wine-derived polyphenols) to reduce cardiovascular events have been disappointing.[57]

Conclusions

The rates of vascular and total mortality are lower for people who drink low to moderate

amounts of alcohol than for those who do not drink at all or drink heavily.

The cardioprotective nature of alcohol has been attributed to both its antithrombotic properties and its ability to increase HDL-cholesterol levels. Moreover, wine – especially red wine –, due to its polyphenol content, might offer additional advantages and greater cardiovascular benefits than alcohol alone. In fact, polyphenols might reduce atherosclerosis by inhibiting lipoprotein oxidation and thrombosis independently of alcohol. Some believe this explains why France has a lower rate of CHD than the United Kingdom ("French paradox"), while it remains unclear whether red wine has any advantage over other forms of alcoholic beverages. On the other hand, grape juice contains the same polyphenol compounds as red wine and seems to produce the same biologic effects, but at higher liquid volumes.[58]

Available epidemiological data – mainly if not exclusively based at the moment on observational studies – confirm the hazards of excess drinking, but also indicates the existence of potential windows of alcohol intake which may confer a net beneficial effect of drinking, at least in terms of survival, both in males and in females. Methodological limitations of observational study design, the role of uncontrolled confounding and the optimal choice of the referent group are important issues to be considered in future studies on alcohol and health.[59]

Randomized controlled trials offer a more solid answer than observational studies to many questions in medicine, mainly restricted, however, to the efficacy of drugs; controlled intervention trials on diet in general and on alcohol in particular, are difficult and ethically questionable to perform.[60] One has therefore to rely upon observational studies such as those analysed here or prospective studies where participants spontaneously decrease or stop drinking. Interestingly enough, the first study of the latter type[61] supports the inverse relation of moderate alcohol intake with CVD.

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