Wine, alcohol, polyphenols and cardiovascular disease

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Abstract. Excessive alcohol consumption is associated with increased morbidity and mortality as well as with labour and traffic accidents. However, current evidence suggests beneficial effects of moderate drinking on cardiovascular events including coronary heart disease, ischaemic stroke, peripheral arterial disease and congestive heart failure. The underlying mechanisms to explain these protective effects against coronary heart disease include an increase in high-density lipoprotein cholesterol and an increase in insulin sensitivity, and a decrease in platelet aggregation and circulating concentrations of fibrinogen. However, there are discrepancies regarding the specific effects of different types of beverages on the cardiovascular system, and also whether the possible protective effects of alcoholic beverages are due to their alcohol component (ethanol) or non-alcoholic products containing, mainly polyphenols. Recent randomised clinical trials have shown that wine, a polyphenol-rich alcoholic beverage, provides higher antioxidant and anti-inflammatory effects than some spirits such as gin, a polyphenol-free alcoholic beverage. In addition, dealcoholized red wine decreases blood pressure through a nitric oxide mediated mechanism, suggesting a protective effect of polyphenols on vascular function. Other studies performed in women have observed that daily doses of 15–20 g of alcohol as red wine are sufficient to elicit protective effects similar to those observed in men who consumed higher doses of wine. In conclusion, moderate consumption of wine exerts a protective effect on biomarkers related to the progression and development of atherosclerosis due to its alcoholic (ethanol) and non-alcoholic (polyphenols) content. Women are more sensitive to the beneficial effects of wine.

Keywords: Wine, alcohol, polyphenols, cardiovascular disease, oxidative stress, inflammation

1. Introduction

The healthy effects of wine are known from ancient times. In fact, wine has been used in old medicine as an antiseptic, a painkiller and as a treatment for several dermatological and digestive disorders [46]. In addition, wine has been closely associated with healthy diets, particularly in Mediterranean countries [49] and many people have attributed great benefits to wine consumption with no scientific basis. The first modern evidence of a scientific link between alcohol consumption and cardiovascular disease was made in the early part of the last century, when it was observed in necropsy studies that individuals that died from alcoholic cirrhosis had cleaner arteries than they ought to according to their age and lifestyle habits, suggesting that alcohol could exert a protective effect against atherosclerosis. Many years later, in the 1970s, several researchers started to scientifically study the relationship between alcohol consumption and overall mortality or other hard end-points such as coronary heart disease [12], stroke [34], peripheral arterial disease [35] and heart failure [16]. The overall conclusion
of these studies is that people consuming one to two standard drinks per day showed a lower cardiovascular event rate than subjects abstaining from alcohol and those with high alcohol intake [47], a relationship described as J-shaped (or U-shaped) curve [11, 56].

Most of these epidemiological studies correlating moderate alcohol intake with protector effects on the cardiovascular system did not take into account the type of beverage consumed. However, after the description of the French Paradox 20 years ago, part of the research was focused on the protective effects of moderate wine intake compared to the effects of other alcoholic beverages, mainly beer and spirits. Based on epidemiological data, the term “French Paradox” was used to describe the low incidence of cardiovascular disease and the mortality of French population despite their high intake of dietary saturated fats. This paradox has been attributed to moderate wine consumption by the French population, but it was not related to alcohol (ethanol) contained in wine, since plasma high-density lipoprotein cholesterol (HDLc) concentrations were similar to those observed in other countries with a higher prevalence of coronary heart disease that consume mainly other alcoholic beverages [44]. From the beginning, the French Paradox received several criticisms [6, 32], opened an interesting debate as to which type of alcoholic beverage is more cardioprotective than the others and triggered several studies on the effects of the different components of red wine, mainly alcohol and polyphenols on the health, but especially on cardiovascular system. However, the debate continues; the key question related to alcoholic beverages continues to be whether the beneficial effects of moderate consumption of alcoholic beverages is due to ethanol, to their polyphenolic content, or both.

2. Negative effects of alcoholic beverages

It is always important to remember that excessive alcohol intake induces the appearance of several chronic diseases including chronic alcoholism, liver disease, pancreatitis, different types of encephalopathy and neurodegenerative diseases, peripheral neuropathy, myopathy and also cardiomyopathy (Table 1). In fact, chronic alcohol intake gives rise to acute and chronic effects on the cardiovascular system. Among the acute effects, the most frequent action of ethanol on the heart is to induce cardiac arrhythmias. Clinicians have long recognized the temporal association of binge drinking and the onset of atrial fibrillation, especially during weekends, a disease known as the “holiday heart syndrome”. In addition, high alcohol intake may provoke ventricular tachyarrhythmias and sudden death. A quarter of the young or middle-aged adult sudden deaths are related to an overdose of alcohol, especially in those who suffer from a subclinical cardiomyopathy [24]. On the other hand, the main chronic effects of maintained high ethanol intake on the cardiovascular system are dilated cardiomyopathy and arterial hypertension. The development of an alcoholic cardiomyopathy requires the consumption of high amounts of ethanol during more than 10 years. In our experience, the first clinical features of alcoholics with dilated cardiomyopathy is usually observed when the subject have drunk a total lifetime dose of ethanol higher than 20 kg of ethanol/kg of body weight [57]. High alcohol intake also produces an increase of blood pressure, whereas alcohol abstinence reduces systolic and diastolic blood pressures to normal or near normal values [18]. In the Framingham study the prevalence of hypertension was double in people who consumed great amounts of alcohol compared with the moderate consumers. However, not all who have consumed high amounts of alcohol develop dilated cardiomyopathy. Great individual vulnerability has been reported in the toxic effects of alcohol. Thus, women and relatives of patients with alcoholic cardiomyopathy have a higher prevalence of cardiac dysfunction compared to men or non relatives who have consumed the same amounts of alcohol [58]. This individual vulnerability to the organic injuries by alcohol has been attributed to some genetic characteristics of the subjects. As an example, a close relationship has been observed between alcoholic cardiomyopathy and polymorphism of the gene of the angiotensin-converting enzyme [21].

3. Positive effects of moderate wine consumption on cardiovascular system

On the other hand, several studies have shown that moderate alcohol consumption mainly in the form of wine could have beneficial effects (protective) on health (Table 1). Up to now, the cardioprotective effect of moderate consumption of wine or alcohol has been documented in several ecological, epidemiological, necropy, case-control and cohort studies performed
Positive (moderate intake) and negative effects (excessive intake) of patients with established heart disease or at high-risk more recent cohort studies have confirmed that, among lower mortality by cardiovascular disease. Results of between low or moderate consumption of wine and a high significant relation in the east of France [44] found a high significant relation whereas in some European studies such as the Copenhagen City Heart Study [22] or the one carried out in Hagen City Heart Study [22] or the one carried out in Hol. Interestingly, the results of the studies differed depending on the continent where were performed. Thus, in many epidemiological studies from United States, especially those based on the registries of the cohort trials. However, interventional clinical trials regarding alcoholic beverages must contemplate several ethical considerations and the length of these studies is limited because of the personal difficulties to accomplish interventions, thus, well-designed randomized clinical trials which evaluate hard end-points may be due to different confounding factors difficult to strictly control in even prospective cohort studies. Thus, the pattern of drinking is absolutely different in Mediterranean countries form Anglo-Saxon countries [48] and, more important, wine drinkers usually consume healthy foods compared to beer and liquor drinkers [25].

The best way to solve these discrepancies is to perform randomized clinical trials that allow an optimal control of these confounding factors. In addition, the scientific evidence of these trials is higher than that of the cohort trials. However, interventional clinical trials regarding alcoholic beverages must contemplate several ethical considerations and the length of these studies is limited because of the personal difficulties to accomplish interventions, thus, well-designed randomized clinical trials which evaluate hard end-points as final variables are warranted. In the meanwhile, randomized clinical trials that evaluate intermediate markers of cardiovascular risk allow us to assess the differences in effects of the different alcoholic beverages on the cardiovascular system, always within the context of moderate intake.

4. Insulin sensitivity and type 2 diabetes mellitus

Diabetes mellitus is one the main risk factors of cardiovascular disease. Two meta-analyses of 15 and 20 cohort studies [3, 40] pointed out that moderate drinkers show a lower incidence of type 2 diabetes mellitus than lifetime abstainers or excessive consumers, with an apparent J-shaped association. This effect seemed to be independent of the type of alcoholic beverage consumed. However, in other prospective studies, the inverse association between moderate alcohol consumption and lower diabetes risk was most apparent in women who reported to drink preferentially wine or beer than in those who consumed liquor [60]. This beneficial effect has been related to improved insulin sensitivity enhancing insulin secretion, pancreatic β-cell survival and/or glucose uptake by peripheral tissues, among others.

However, the results of clinical studies examining the effects of moderate alcohol intake and the different
types of alcoholic beverages have been inconsistent. Some studies have reported no significant changes in insulin sensitivity after intake of wine or spirits [4, 36, 51], whereas others have reported an improvement with any beverage [14, 27]. In this respect, a recent randomized trial performed in high-risk men, moderate dealcoholized red wine and red wine, but not gin significantly improved insulin sensitivity [9], suggesting that polyphenols may play a key role in the prevention of diabetes. In fact, intervention studies with grapes and grape seed extract improved glycemic status in type 2 diabetic patients [38, 62]. Thus, moderate alcohol intake, mainly in the form of wine, helps to maintain or even improve insulin sensitivity. However, more studies are warranted on this issue.

5. Lipid effects

Increase of plasma HDL-cholesterol is the most well-described effect of moderate alcohol consumption, and until recently, this was considered as the main protector effect of alcohol intake on cardiovascular system. This effect is observed after the consumption of any alcoholic beverage in a dose-dependent manner, and, accordingly, it is considered to be due to ethanol itself [5]. Ethanol also seems to increase ApoA-I and II [9, 20]. The effects on triglycerides, LDL-cholesterol and lipoprotein (a) are still under debate. There are several limitations analyzing these effects since the different studies performed have different lengths, some variables analyzed have a longer half-life time than that analyzed, especially in cross-sectional studies, and differences in the characteristics of the participants, such as age, sex, and cardiovascular risk factors, limit the comparison between studies. However, despite of these limitations, a J-shape increase of presenting high triglycerides was observed among 2014 hypertensive men, with the lowest plasma triglyceride concentrations being found in moderate alcohol consumers [41]. LDL-concentrations do not change after moderate alcohol consumption [5]. In respect to lipoprotein (a), a meta-analysis [5] pointed out that moderate alcohol intake has no effect on this variable, but in two clinical trials performed in healthy men [20] and high-risk subjects [9] adjusted mean lipoprotein (a) was significantly reduced after red wine, but not after gin interventions. Thus, given the paucity of effective therapy for elevated lipoprotein (a), the potential lowering efficacy of ethanol and/or polyphenols deserves further research. However, since grapes, grape juice and grape extracts positively modify cholesterol homeostasis [26, 49] and red wine is more effective than white wine changing lipid profile, wine polyphenols also play a role in lipid changes observed in moderate drinkers [23].

6. Effects on blood pressure and endothelial function

Although the negative effects of heavy and binge alcohol drinking on blood pressure are well known, the effects of moderate alcohol consumption are controversial, since some studies have observed a linear trend and others a non-linear or even a J-shaped association [2, 10]. A meta-analysis has pointed out that alcohol consumption increases the risk of hypertension in dose-dependent manner [54] and reduction of alcohol consumption leads to a decrease in blood pressure also in a dose-response relationship [61]. However, moderate alcohol intake, especially in the form of red wine, seems to reduce blood pressure. In fact, in vitro and experimental studies have shown a blood pressure lowering effect and an enhancement of endothelial nitric oxide production [15]. However these results are difficult to extrapolate to humans since the amount of polyphenols from red wine used in these studies is usually higher than that achieved in plasma through moderate wine intake. In a recent 4-week intervention cross-over clinical trial, moderate doses of dealcoholized red wine decreased systolic and diastolic blood pressure while increasing plasma NO concentration. Red wine tended to have similar effects to those of dealcoholized red wine, but the changes did not achieve statistical significance, and gin had no effect. Thus, these blood pressure-lowering effects and NO-raising effects should be attributed to red wine polyphenols and not to alcohol [7].

On the other hand, the effects of moderate alcohol intake on endothelial function remain controversial. In a multiethnic cross-over study, those subjects who drank between >1 drink/month and 2 drinks/day showed a higher flow-mediated dilatation (FMD) than non drinkers or those who drank more than 2 drinks/day, independent of the type of alcoholic beverage consumed [52]. However, in randomized intervention trials, 30 g of alcohol as red wine showed significant beneficial effects on endothelial function 1–4 h after ingestion, while beer and white wine had a borderline effect and whiskey exerted no effect [55].
In other studies either red wine and dealcoholized red wine decreased plasma endothelin-1 concentration [39]. Thus, it seems that red wine polyphenols exert a beneficial effect on endothelial function but this effect do not persist >4 h.

7. Thrombosis and fibrinolysis system

Heavy alcohol intake has been associated with lower fibrinolytic capacity, a more procoagulant state and a higher blood viscosity, whereas moderate alcohol consumption is consistently associated with a decreased procoagulant state and blood viscosity, as well as a higher fibrinolytic capacity. In a meta-analysis, consumption of less than 12 g of ethanol/day was significantly associated with a decreased relative risk of total stroke [45]. In addition, in population studies, alcohol consumption was associated with a reduced risk of venous thrombosis and lower fibrinogen levels [42]. In randomized clinical trials, plasma fibrinogen levels decreased after red wine and gin intake, suggesting that this effect is due to ethanol contained in alcoholic beverages [20]. Other positive effects of moderate alcohol intake on hemostatic system include inhibition of platelet aggregation and reduction of concentration of tissue factor and factors VII, VIII and VII-von Willebrand. Wine, by itself, also increases plasminogen activator-1/plasminogen activator (PAI-1/tPA) ratio. Therefore, the anticoagulant effect of moderate alcohol consumption seems to be effective in both healthy subjects and patients with a pro-coagulant profile. However, a linear relationship between increased alcohol consumption and risk of hemorrhagic stroke was also observed.

8. Mechanisms of the cardioprotective effect of moderate wine intake

The beneficial effects of moderate wine intake on the cardiovascular system have been related to their action on oxidative status and inflammation of the arterial wall.

8.1. Oxidative status

While alcohol itself is known to induce oxidative stress, several in vitro studies regarding polyphenols from wine, beer, and vegetables have shown that these compounds exert an antioxidant effect. Accordingly, it seems that there are a countering effect between polyphenols and alcohol. Several clinical trials have shown that red wine increases plasma antioxidant capacity, suppresses reactive oxygen species generation, reduces plasma malondialdehyde, prolongs lag phase time of low-density lipoprotein (LDL) particles and decreases oxidative DNA damage [20]. By contrast, ethanol decreases antioxidant and increases lipoperoxidation serum parameters [1]. In addition, a postprandial reduction of oxidative stress has also been observed after red wine consumption [13], an interesting effect that help to promote the consumption of wine always with meals.

8.2. Inflammation

Atherosclerosis is considered a low-grade inflammatory disease. In a meta-analysis [5], the association between alcohol intake and plasma concentration of different inflammatory biomarkers related to atherosclerosis, such as C-reactive protein (CRP), interleukin 6 (IL-6) and tumour necrosis factor-alpha (TNF-a) was not significant. However, when the type of alcoholic beverage was considered, the results differed. In a 4-week randomized cross-over trial, red wine and gin decreased IL-1, but only red wine but not gin diminished plasma CRP in healthy subjects [19], explaining why CRP is not affected when only alcohol is considered. In addition, the effects are not the same in high-risk vascular subjects, since alcohol (red wine and gin) increased the anti-inflammatory IL-10 and decreased IL-16, and red wine but not gin decreased plasma IL-6 concentration [8].

Cell adhesion molecules and cytokines are other inflammatory biomarkers related to atherosclerosis since these molecules participate in the recruitment of circulating leukocytes to the vascular endothelium and further migration to subendothelial spaces, initiating the atherosclerotic process. In healthy volunteers [19] significant reductions of vascular cellular adhesion molecule-1 (VCAM-1), intercellular CAM-1 (ICAM-1), very late antigen-4 (VLA-4) lymphocyte expression and lymphocyte function associated antigen-1 (LFA-1), macrophage-1 antigen (Mac-1), VLA-4 and monocyte chemoprotein-1 (MCP-1) monocyte expression were observed after red wine, but not after gin intake. Again, the effects in high-risk subjects were different but protective [8].
Table 2
Mechanisms of the positive and negative effects of the moderate consumption of alcoholic drinks with (wine) and without (gin) polyphenols [15]

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<tr>
<th>Effects of Alcoholic Drinks without Polyphenols (GIN)</th>
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<th>Negative</th>
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<td><strong>On lipoproteins</strong></td>
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<td>Increase in HDL-cholesterol</td>
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<td>Reduction of lipoprotein a</td>
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<td>Reduction of the oxidation of LDL-cholesterol</td>
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<td>Increase in the sensitivity to the insulin</td>
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<td>On the inflammation markers</td>
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<td>Reduction of C-reactive protein</td>
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<td>On haemostasis</td>
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<td>Reduction of platelet aggregation</td>
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<td>Reduction of factor VII, VIII and VIII-von Willebrand</td>
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<th>Effects of Alcoholic Beverages with Polyphenols (WINE)</th>
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<td><strong>On lipoproteins</strong></td>
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<td>Reduction of molecules of adhesion LFA-1, Mac-1, VLA-4 and chemokine MCP-1 in circulating monocytes Inhibition of nuclear factor κB Reduction of fibrinogen On the haemostasis Reduction of platelet aggregation Reduction of the tissue factor Reduction of factor VII, VIII and VIII-vW Increase in the tissue factor of plasminogen Increase in the activity of PAI-1 On the vascular function Increase in the coronary vasodilatation induced by adenosine</td>
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9. Summary

Although heavy or binge alcohol consumption leads to an increase in the risk of all-causes death and makes up an enormous social and economical problem that must be addressed, moderate alcohol consumption, especially in the form of wine, has cardioprotective effects through different mechanisms. Moderate wine consumption improves glucose metabolism, lipid profile, endothelial function and coagulation and platelet function throughout their anti-oxidant and anti-inflammatory effects (Table 2). All these protective effects explain the reduction in overall and cardiovascular mortality of moderate wine drinkers reported in some epidemiological studies. Nevertheless, although they are hard to carry out and need careful ethical considerations, more long-term clinical trials are needed to elucidate whether other mechanisms may be involved.
in these protective effects and which type of alcoholic beverage is more cardioprotective with the highest level of scientific evidence.

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