Alcohol and Atherosclerosis

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Observational studies have attributed a protective effect to alcohol consumption on the development of atherosclerosis and cardiovascular morbidity and mortality. Alcohol intake in the amount of one to two drinks per day results in an estimated 20-40% reduction in cardiovascular events. An additional protective effect, according to major cohort studies, has been attributed to wine, probably due to antioxidant effects and platelet antiaggregation agents. On the other hand, the influence of different patterns of alcohol consumption and environmental factors may explain a great part of the additional effect of wine. Protection may be mediated by modulation of other risk factors, because alcohol increases HDL-C, produces a biphasic response on blood pressure, and modulates the endothelial function, while it neither increases body weight nor impairs glucose-insulin homeostasis. Alcohol may also have a direct effect on atherogenesis. Despite these favorable effects, the current evidence is not enough to justify prescribing alcohol to prevent cardiovascular disease.

In recent years, the idea that regular alcoholic beverage consumption protects against cardiovascular diseases has been spread. Physicians, and more particularly cardiologists, are frequently asked about the veracity of this statement.

The cardiovascular diseases resulting from atherosclerosis are a challenge due to their epidemiological importance and the multifactorial features involved in their genesis. Many risk factors of atherosclerosis have been clearly identified, and some, such as hypertension [1], dyslipidemia [2], and diabetes mellitus [3], are amenable to effective interventions. The intensity of the association of other risk factors, however, has not been clearly established. The effect of alcoholic beverage consumption on the incidence of atherothrombotic diseases is a particular case among them. This is due not only to the intensity of the effect but also to the interaction with other risk factors making it difficult to grasp the real impact, be it beneficial or deleterious.

The habit of alcoholic beverage consumption is widespread and accepted in most countries. Ethanol available in different forms and its pattern of consumption is widely varied in population groups. Despite methodological difficulties in quantifying and classifying the amount of alcohol ingested and on the basis of a population study carried out in Porto Alegre [4], it is estimated that approximately 15% of the population have alcoholic beverage consumption above 30mg/day. In addition, it is suggested that the rate of abusers is proportional to the total consumption of the population [5]. It is worth noting that abstainers and social consumers comprise three quarters of the population. In this latter group of individuals, understanding the interrelations between alcohol consumption and health may have a greater epidemiological impact.

Protection provided by alcohol consumption – Several population-based studies [6-8] suggest that moderate consumption of alcoholic beverages protects against coronary artery disease and cardiovascular disease.

In regard to cerebral strokes, a probably protective effect against ischemic events exists [9-11], but the effect on hemorrhagic events is inconsistent [9,11].

Despite the presumable benefit provided by alcoholic beverage consumption on the incidence of cardiovascular disease, the sequelae of alcohol intake are among the 20 major causes of loss of disability-adjusted life years [12]. In addition, alcohol consumption increases mortality due to neoplastic diseases, diseases of the digestive tract, and external causes [13,14].

An overview assessment in most of the countries where the subject has been studied shows that mortality is still lower among those with moderate alcohol consumption, mainly in populations with a higher cardiovascular risk [14], (fig. 1) and in secondary prevention in patients suffering from myocardial infarction [15]. On the other hand, heavy consumption of alcoholic beverages (more than 3 drinks a day) may be associated with an increase in mortality among men who have already experienced myo-

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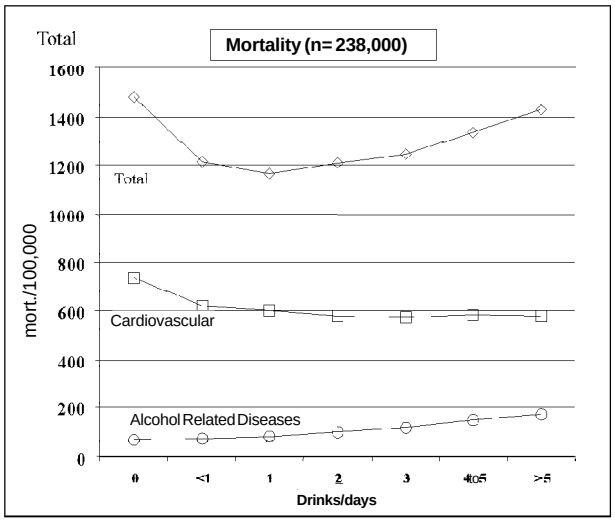

Fig. 1 - Mortality curve for different causes and alcohol consumption. (Adaptation from Thun. N Engl J Med 1997; 337: 1705).

cardial infarction [16].

Summarizing, evidence exists suggesting that consumption of 1-2 drinks of alcoholic beverages per day causes a 20-40% reduction in cardiovascular events as compared with that of abstainers, and a progressive increase in diseases attributed to consumption of higher levels of alcohol is observed.

Controversies about the benefits of alcohol consumption

Types of beverages – Some studies suggest a greater reduction in cardiovascular mortality among wine consumers, as well as fewer hospitalizations due to coronary artery disease [17] and a reduced incidence of cerebral strokes [10] among these individuals. In addition, moderate wine consumption seems not to be associated with an increase in the risk of cancer of the upper digestive tract, unlike beer and distilled spirits [18].

The hypothesis of the additional protective effect of wine is mainly based on two types of evidence. Studies where alcohol consumption and clinical events were measured as means or population ratios, usually called ecological studies [19-21], showed a reduced incidence of coronary events in populations with a relatively high consumption of saturated fat concomitantly with high alcohol intake, mainly in the form of wine. This phenomenon is known as the French paradox. This type of evidence, despite the consistent results in the mentioned studies, makes impossible the identification of the direct relation between exposure to factors of interest – consumption of alcohol and saturated fat – and occurrence of clinical events among the populations studied. The second type of evidence is the experiment showing the biological effects of flavonoids and polyphenols present in wine [22], which are mechanisms supposedly responsible for the reduction of thromboembolic events [23]. Recently, a French cohort study [24] showed that the reduction of total and cardiovascular mortality was more pronounced (30-40% reduction in the risk) in those individuals with regular and exclusive wine consumption. This is consistent evidence even though it has not been corrected for the other potential factors present in wine consumers, who comprise most of the population.

Environmental factors – Rimm et al [8], reviewing ecological, cohort and case-control studies, reported that not only wine, but also beer and distilled spirits may have a more intense protective effect in certain populations. These effects are thought to be associated with the type of beverage most used in the regions. These findings suggest that maybe it is not the type of the beverage but the social and demographic, cultural, or even alimentary features [25] associated with alcohol consumption that are the real protectors against cardiovascular disease. Wannamethee and Shaper [26] compared the protective effect of different types of alcoholic beverages in a certain population and identified that a great part of the additional benefit attributed to wine could be explained by a lower prevalence of other risk factors, such as smoking, obesity, and sedentary lifestyle. The importance of the diet has also been shown in Lyon Diet Heart Study [27] of secondary prevention, where the use of a Mediterranean diet managed to reduce the incidence of new infarctions by approximately 70%. Therefore, the moderate consumption of alcoholic beverages typical of a certain society could be an indication of healthy behavior and not a real protective mechanism.

We may also consider that part of the increased risk in absteiners may correspond to individuals who stopped drinking because they were ill. This issue was assessed in several studies [6,9,14,28], which did not significantly change the original estimates. On the other hand, a reduction from an excessive alcoholic consumption to a moderate regular consumption, potentially associated with a healthier lifestyle, is more difficult to quantify.

Patterns of consumption – Even though laboratory evidence supports the protective effect of wine, other findings suggest that not the type of alcoholic beverage but its form of consumption modifies cardiovascular risk. Studies suggest that alcoholic beverage consumption in an excessive and sporadic manner is associated with cardiac arrhythmias [29] and with a higher incidence of cerebral strokes [30] and of acute coronary artery events [31], which are not supported by another study [32]. However, in most studies, alcohol consumption is measured through questions about the mean consumption, limiting the recognition of the effects related to the forms of consumption on cardiovascular disease. On the other hand, the drinking pattern may vary with the type of alcoholic beverage, and a moderate and regular consumption is usually observed in wine consumers [26,33].

Another significant issue in regard to the pattern of consumption is that the usual consumption reported by European studies is substantially higher than that reported by American studies. One could speculate that the same mean alcoholic intake may correspond to a pattern of con-

sumption considered moderate/regular in studies with greater consumptions, but may correspond to a pattern of occasional and isolated consumption of greater amounts in populations with a usually lower consumption.

Temporal bias – Recently, a new hypothesis has been formulated by Law and Wald [34] in an attempt to explain the French paradox. They showed that cholesterol levels and ischemic events correlate with the consumption of saturated fat from past decades (which corresponds to the time necessary for the development of atherosclerotic disease). They also showed that the disproportion between levels of cholesterol and ischemic events usually attributed to wine consumption is due to the recent increase in the saturated fat intake in Mediterranean countries.

Effects of alcohol on cardiovascular risk factors

Lipoproteins – Change in lipoproteins is the most often described mechanism mediating cardiovascular protection associated with alcohol intake. Population-based evidence shows higher levels of HDL-C in individuals drinking alcoholic beverages [35,36]. However, only 50% of the protective effect may be explained by an increase in HDL-C [28].

Alcohol affects the metabolism of lipoproteins in different phases. Regular consumption may be associated with an increase in the synthesis of lipoproteins [37], a reduction in the degradation of HDL-C, and a higher hepatic metabolism of LDL-C[36]. In the postprandial period, alcohol accounts for an additional increase in the serum levels of triglycerides with inhibition of the oxidation of free fatty acids [38]. It also modifies the dynamics and the metabolism of the lipoproteins of HDL-C [36]. The higher amount of lipids aggregated to lipoproteins with alcohol consumption in the postprandial period may result in increased tissue removal through an increase in the mobilization of cholesterol esthers and triglycerides [37,39].

It is worth emphasizing that in individuals with coronary heart disease, postprandial increased serum levels of triglycerides are higher and more prolonged [40]. An increase in serum levels of triglycerides and an increase in free fatty acids are associated with a reduction in endothelial vasodilation in healthy [41] and insulin-resistant [42] individuals.

Inflammation and endothelial dysfunction – An excessive consumption of alcoholic beverages has long been associated with a reduction in immunity probably because of a lower activity of leukocytes and cytokines. On the basis of laboratory experiments, alcohol has been shown to also affect vascular reactivity. Ethanol may reduce vasodilation mediated by endothelium in rat mesenteric capillaries [43]. On the other hand, in humans the acute vasodilating effect of alcohol is associated with a reduction in peripheral resistance [44]. The hemodynamic effects of wine may be secondary to antioxidant effects [45,46], induction of the sythesis of nitric oxide [47], and endothelium-mediated vasodilation [45], in addition to its effects on platelet aggregation [48], and plasminogen activation [49,50]. Experimental models have shown an inhibition in formation of atherosclerotic plaques with administration of wine or its nonalcoholic components [51]. Even though tempting, these clinical effects have only been demonstrated in small samples with no representation of its potential clinical relevance in population studies.

Hypertension – Excessive alcohol consumption has been associated with systemic hypertension. On the basis of prospective studies, a direct causal relation has been suggested, and a higher incidence of elevated blood pressure levels has been shown in individuals who drink excessively [52-54] and in alcoholic hypertensive patients, whose pressure levels decrease when they undergo reduction in alcohol intake [55].

Generally, the consumption of 1-2 drinks per day for men and half of this amount for women is not associated with a significant increase in blood pressure levels [52-54,56,57], and some studies even show lower pressure levels in these individuals [52,56,57].

Another not well understood phenomenon is the dissociation between acute vasodilating effects with isolated alcohol administration [58-61] and its chronic hemodynamic effects. Isolated alcohol consumption may cause an acute reduction in blood pressure with a possible dose-dependent rebounding aftereffect in healthy individuals [62] and reduction in the usual circadian variation in hypertensive obese individuals, when alcohol is ingested at lunch [63]. This mechanism may help understanding the higher blood pressure levels between 13 and 24 hours after the last alcoholic intake observed in a population study [64]. Sympathetic modulation, cortisol, the renin-angiotensin system, and endothelial activity are mechanisms potentially implicated in these effects. Changes in these different homeostatic mechanisms may be another link between alcohol effects and cardiovascular disease.

Smoking – Smoking is one of the changeable factors that most increase the absolute risk of cardiovascular events [65]. A positive association between smoking and the amount of alcohol intake is also observed [66,67]. Therefore, we can speculate that the protective effects of regular alcohol intake may be minimized by the risk associated with an increase in smoking.

However, in a Finnish study [35] with a limited number of cardiovascular events analyzed, the authors observed that the protective effect associated with alcohol consumption was limited to smokers. This may be explained by the highest absolute risk in smokers, which increases the potential benefits of protective factors.

Obesity – Moderate regular alcohol consumption is not associated with an increase in the incidence of obesity [66,68,69], and a specific protective effect against central obesity may exist in obese wine consumers [70].

In a crossover experiment [71], moderate wine consumption (270mL/day) changed neither the weight nor the meta-

Table I - Relative changes in the levels of risk factors associated with alcohol consumption (g/day) in different studies (absolute values in absteiners as reference)

	Abstainers	0-0,5	0,5-1	1,0-2,0	8,0-16,0	16,0-24,0	24-32	>32	>100
HDL-C									
Gordon[66]	1			1,02	1,08	1,13	1,17	1,26	
Mänttäri[35]	1	1,01	1,02	1,07	1,12				
Savolainen[36]	1					1			1,12
Blood pressure									
Gordon[57]	1			0,99	1,01	1,02	1,02	1,03	
Smoking (%)									
Gordon[57]	1			1,22	1,35	1,6	1,7	1,9	
Mänttäri[35]	1	1,3	1,6	1,8	2,4				
Weight									
Gordon[66]	1			0,98	0,97	0,97	1	1,01	
Glycemia									
Gordon[57]	1			0,97	0,99	0,99	0,98	0,98	
Lazarus[78]	1			0,99		0,99		1,01	
Diabetes (%)									
Rimm[67]	1			1,2	0,92	0,93	0,95	0,7	
Stampfer[75]	1			0,8	0,8	0,6			
Carotid thickening									
Kiechl[85]	1					0,8		0,4	2,2

bolic substrate of individuals. Another study [72], using indirect calorimetry, showed an expenditure of approximately 20% of the energy present in alcohol in thermogenesis induced by alcohol, adding to the evidence that the caloric component of alcohol is not used in maintaining body weight [73,74].

Diabetes mellitus and insulin resistance – Moderate alcohol consumption is associated, in some studies, with a lower incidence of diabetes mellitus [67,75], hyperinsulinemia [76,77], and insulin resistance [78,79]. Vasodilation caused by alcohol may provide an increase in peripheral glucose uptake in these states of reduction in peripheral homeostasis of glucose and insulin [80].

Just one single study [81] showed worsening in the metabolic control of diabetic patients, which was normalized in a short period of abstinence, but these individuals used a mean of 4 drinks of alcoholic beverages per day. However, acute moderate alcohol consumption does not cause a significant clinical worsening of the metabolic control [82,83].

Independently from the direct effect of alcohol consumption on the metabolism of glucose and insulin, the protective effect on coronary heart disease in type II diabetic patients is at least similar to that in nondiabetic individuals [84].

Atherogenesis – Even considering the individual effect on risk factors in a population with high alcohol consumption [85], an association between alcohol intake and the degree of carotid thickening has been observed. Considering that the results of this study were controlled as to weight, social activity, blood pressure, triglycerides, fibrinogen, glycemia, LDL-C, and HDL-C, it was suggested that alcohol might have a direct effect on the development of atherosclerotic disease, with a maximum protective effect when consumption was between 1 and 50g/day of alcohol. The risk was increased with a mean consumption above 200g/day (table I). Another study [86] on usually lower alcohol consumption (approximately one drink per day) has not shown the same protective association.

Conclusion

Comprehension of the innumerable effects of alcoholic beverage intake, a widespread habit among us, on risk factors and cardiovascular disease itself is fundamental for developing strategies and interventions aiming at reducing morbidity and mortality.

Regular alcohol intake is clearly associated with a reduction in cardiovascular events. The significance of this benefit, however, may have diverse clinical implications depending on other factors present, which may partially account for the effects attributed to alcohol. Regular alcoholic beverage consumers, mainly at middle age and with other risk factors for cardiovascular diseases, seem to be more protected against these diseases.

Even though the protective effects of alcohol consumption are potentially real and direct, recommendation for the regular use of alcohol should be based on clinical experiments we lack randomized clinical trials confirming the benefits shown in observational studies. We should also take into consideration potential individual and social risks secondary to the deleterious effects of widespread alcoholic beverage consumption. Decisions in individual cases should be based on reasoning and common sense, considering that we really do not know the actual effectiveness of alcohol consumption as a protective factor against cardiovascular diseases.

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