

Alcohol consumption, cardiovascular health, and endothelial function markers

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Abstract

Cardiovascular diseases are among the worldwide leading causes of shorter life expectancy and loss of quality of life. Thus, any influence of diet or life habits on the cardiovascular system may have important implications for public health. Most world populations consume alcoholic beverages. Since alcohol may have both protective and harmful effects on cardiovascular health, the identification of biochemical mechanisms that could explain such paradoxical effects is warranted. The vascular endothelium is the target of important mediating pathways of differential ethanol concentrations, such as oxidative stress, lipoproteins, and insulin resistance. Alcohol-induced endothelial damage or protection may be related to the synthesis or action of several markers, such as nitric oxide, cortisol, endothelin-1, adhesion molecules, tumor necrosis factor alpha, interleukin-6, C-reactive protein, and haemostatic factors. The expression of these markers is consistent with the J-shaped curve between alcohol consumption and cardiovascular health. However, there is genetic and phenotypic heterogeneity in alcohol response, and despite the apparent beneficial biochemical effects of low doses of ethanol, there is not enough clinical and epidemiological evidence to allow the recommendation to consume alcoholic beverages for abstemious individuals. Considering the potential for addiction of alcoholic beverage consumption and other negative consequences of alcohol, it would be worthwhile to identify substances able to mimic the beneficial effects of low doses of ethanol without its adverse effects. © 2007 Elsevier Inc. All rights reserved.

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Alcohol and cardiovascular disease

The inverse correlation between moderate alcohol consumption and coronary mortality has long been recognized (Albert et al., 1999; Belleville, 2002; Klatsky, 2002; Rimm et al., 1999). The term “French paradox” was coined by epidemiologists to call attention to the relatively low rate of coronary disease among the French, despite the heavy consumption of saturated fats (Artaud-Wild et al., 1993; Belleville, 2002; Tunstall-Pedoe et al., 1999). However, high doses of alcohol increase the risk of mortality due to several causes, including cirrhosis and cancer (Friedman and Kimball, 1986; Marmot et al., 1981; Renaud et al., 1998). This results in a J-type curve between mortality and alcohol

consumption (Klatsky et al., 1992). Beneficial effects of the consumption of low to moderate amounts of ethanol have been postulated. According to the U.S. Department of Agriculture/U.S. Department of Health and Human Services Dietary Guidelines (U.S. Department of Health and Human Services and U.S. Department of Agriculture, 2005), based on a report of U.S. National Institute on Alcohol Abuse and Alcoholism (Gunzerath et al., 2004), moderate drinking of ethanol corresponds to 1–2 drinks per day (15–30 g of alcohol), which is the amount associated with the lowest all cause mortality.

The relationship between alcohol consumption and blood pressure is complex, reproducing the relationship between drinking and cardiovascular disease in general. Heavy alcohol consumption is an established risk factor for hypertension. A study showed that daily alcohol consumption increases systolic blood pressure by approximately 2 mmHg, in normotensive men who take four doses of alcohol, either as

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red wine or beer (Zilkens et al., 2005). Commenting on this study, Fuchs (2005) argues that the vasopressor effect of chronic alcohol use observed even at moderate doses, calls for caution in interpreting the studies that indicate reduction of alcohol-related cardiovascular risk.

Paradoxically, alcohol consumption appears to reduce the risk of myocardial infarction among hypertensive patients (Beulens et al., 2007). The response of blood pressure to alcohol occurs in two phases. While in the first hours after consumption there is arterial dilation accompanied by hypotension, approximately 11–13 h after consumption a higher than baseline blood pressure may be detected (Abe et al., 1994; Bau et al., 2005; Rosito et al., 1999).

Data from the WHO-MONICA project (Kuulasmaa et al., 2000; Tunstall-Pedoe et al., 2000) demonstrated a decreasing gradient in the frequency of coronary events, from north to south in Europe. The highest frequency was found in Scotland and the lowest in Spain and Southeast France. The lower frequency of coronary events in France and other Mediterranean countries was associated with a risk score comparable with that found in populations from other developed countries. However, it is not yet known why there is a lower rate of coronary events in the Mediterranean populations. Although wine is only one of the components of the diet in this population, it was suggested that it might have a beneficial effect against coronary disease (Marmot et al., 1981).

Despite these favorable effects of wine, there is no consensus as to the type of beverage (wine, beer, or liquors), as well as the amount that produces the putative benefit of alcoholic beverages (Di Castelnuovo et al., 2002; Goldberg et al., 2001; Klatsky et al., 1997). To determine the possible beneficial effects of the alcoholic and nonalcoholic components of red wine (e.g., polyphenols), a study compared wine, a solution with the same amount of alcohol, and red wine without alcohol (Senault et al., 2000). There was a slightly higher beneficial effect on the lipid levels when there was moderate consumption of red wine with alcohol, probably due to the action of alcohol and polyphenols on the lipoproteins. The antioxidant effect of several compounds present in grape skin, such as resveratrol, quercetin, and tannic acid, decrease low-density lipoprotein (LDL) oxidation and cardiovascular disease. The main difference between red and white wines is the phenolic content, 20 times higher in red wine (Belleville, 2002). However, although there may be specific effects of wine, there are signs of reduction in the risk of coronary disease due specifically to ethanol, independent of type of alcoholic beverage (Goldberg et al., 2001).

Beulens et al. (2007) suggested a hypothesis to explain both the data focusing on red wine and those that suggest that alcohol consumption in itself would have a beneficial effect. According to the authors, it is possible that the most consumed beverage in a given population is the one that is most probably involved in the reduction of cardiovascular disease risk in that sample. Thus, they propose that the

inverse association could most likely be due to the effect of alcohol.

Besides the multifactorial nature of the effects of alcohol in the cardiovascular system, a large amount of evidence points toward beneficial and harmful effects of alcohol consumption particularly in endothelial function. The resulting endothelial effects are then related to the levels of several markers that reflect the J-shaped curve.

Endothelial function: general aspects and clinical evaluation

The endothelial layer of the vascular wall has endocrine characteristics, producing substances that act locally and remotely in several parts of the organism (Furchgott and Zawadzki, 1980; Vapaatalo and Mervaala, 2001). The endothelium is sensitive to changes in blood flow, blood pressure, inflammatory signs, and circulating hormones, with a capacity to integrate hemodynamic and humoral signs and to modulate the vasomotor tone according to the local tissue metabolic needs.

Endothelial dysfunction precedes the formation of atherosclerotic plaque and has a predictive value for the development of cardiovascular diseases (Schachinger et al., 2000). The evaluation of flow-mediated, endothelium dependent dilation (FMD) and endothelium independent, nitroglycerin-mediated dilation (NFMD) by ultrasound is a noninvasive validated method for measuring endothelial function (Corretti et al., 2002). An impaired endothelial response is associated with risk factors for cardiovascular disease (Vapaatalo and Mervaala, 2001).

Although alcohol abuse has been associated with reduction in FMD (Maiorano et al., 1999; Puddey et al., 2001), this does not appear to occur with moderate drinkers (Zilkens et al., 2003). The main vascular consequence of an acute dose of alcohol is vasodilation (Agewall et al., 2000; Bau et al., 2005; Hashimoto et al., 2001), but there is no consensus as to its action in FMD. While one study (Hashimoto et al., 2001) observed a reduction in FMD after acute alcohol use, others did not find any change (Agewall et al., 2000; Djousse et al., 1999). We have evaluated the early and late effects of alcohol on endothelial function in a homogeneous sample of healthy young men (Bau et al., 2005). A significant vasodilation occurred 4 h after consuming 60 g of alcohol, but there was no late effect (after 13 h) on endothelial function, although a biphasic effect on blood pressure was found, with elevation of blood pressure levels during the final period of observation.

Endothelial function: biochemical markers and the influence of alcohol

The vasodilator effect of alcohol is related to a higher expression of the endothelial nitric oxide synthase (eNOS) (Venkov et al., 1999). However, the effect of alcohol on the

endothelial function itself is more complex. The J-shaped relationship with alcohol consumption reported for cardiovascular risk was also observed for the relationship between alcohol consumption and several inflammatory biomarkers (Thorand et al., 2006).

Whereas moderate consumption is supposed to have a risk-reducing effect reflected on these mediators, alcoholism is associated with endothelial dysfunction and a number of unfavorable outcomes, even among apparently healthy former alcoholics (Di Gennaro et al., 2007). Vasdev et al. (2006) reviewed possible biochemical mechanisms for the beneficial effect of low alcohol doses. The authors suggested that the biochemical pathway for the differential effect of low as opposed to high doses would be related to the ability of low alcohol doses to increase the antioxidant activity, lower insulin resistance, and reduce advanced glycation end products (AGEs), therefore preventing hypertension and atherosclerosis. High doses of alcohol, in turn, would have opposite consequences. Table 1 summarizes the effects of alcohol over several biomarkers of endothelial function.

Oxidative stress

In high concentrations, ethanol is initially metabolized by the microsomal ethanol oxidizing system, creating an oxidative environment. In low concentrations, alcohol is first metabolized by alcohol dehydrogenase, producing reduced nicotinamide adenine dinucleotide from NAD, increasing antioxidant capacity (Vasdev et al., 2006). Other alcohol-induced oxidative stress would result from the production of reactive oxygen species by activation of the mitochondrial electron transport chain, enzymes of the cytochrome P450 complex, and phagocytes (Albano, 2006).

Reactive oxygen species are major initial elements by which high alcohol concentration exerts an inflammatory

action on the cardiovascular system (Wu et al., 2006). Oxidative stress also appears to be the initial factor in the pathogenesis of alcoholic cardiomyopathy. In this case, alcohol appears to act on lipid peroxidation, induce oxidative damage in the mitochondrial DNA, and reduce the antioxidant defenses in the heart (Chicco et al., 2006). Physical exercise attenuates the prooxidant activity of alcohol in the myocardium, probably because exercise stimulates the antioxidant defense system (Chicco et al., 2006).

It is unclear how oxidative stress acts on a whole range of inflammatory process markers. An investigation examined the association between gamma glutamyl transferase, an oxidative stress marker, and the C-reactive protein (CRP) levels in a sample of 12,110 adults (Lee and Jacobs, 2005). There was a positive correlation between the two markers, suggesting that oxidative stress could be a key component of several subsequent reactions associated with chronic inflammation.

The oxidation of LDL plays an important role in the development of atherosclerosis, and oxidized LDL could have a major role in abnormal endothelial relaxation (Steinberg, 1991). Heavy alcohol consumption could be responsible for increased LDL oxidation, since ethanol in high doses is prooxidant (Puddey et al., 2001; Vasdev et al., 2006).

High-density lipoprotein

There is evidence that a significant part of the association observed between alcohol consumption and coronary disease is mediated by an increase in high-density lipoprotein (HDL) cholesterol (Beulens et al., 2007; Mukamal et al., 2005; Rimm et al., 1999). Schafer et al. (2007) evaluated the influence of nonaddictive alcohol consumption on the composition of HDL and its subfractions. Apart from the expected increase in HDL, they also observed

Table 1
The effect of alcohol on biomarkers of endothelial function: a summary of the main vascular effects

Mediator	Effect of alcohol consumption		Adverse vascular effects	Selected references
	Moderate	Higher		
Oxidative stress	Antioxidant	Oxidant	Proinflammatory	Vasdev et al. (2006); Wu et al. (2006)
HDL	Increase	Increase	Unknown	Schafer et al. (2007)
Insulin resistance	Decrease	Increase	Inconclusive	Bell et al. (2000)
Nitric oxide	Increase	Formation of peroxynitrite	Cytotoxicity	Pacher et al. (2007); Puddey et al. (2001)
Cortisol	Blunted response	Blunted response	Unknown	Dai et al. (2007)
Endothelin	Increase	Increase	Increase blood pressure	Soardo et al. (2006, 2005)
Adhesion molecules	Decrease	Increase	Proinflammatory	Sacanella and Estruch (2003)
TNF-alpha	Decrease	Increase	Endothelial dysfunction	Badia et al. (2004); Luedemann et al. (2005)
IL-6	Decrease	Increase	Proinflammatory	Pai et al. (2006)
CRP	Decrease	Increase	Proinflammatory	Raum et al. (2006); Zhong et al. (2006)
Hemostatic factors	Anticoagulant	Procoagulant	Thrombosis	Lee and Lip (2003); Salem and Laposata (2005)

HDL, high-density lipoproteins; TNF-alpha, tumor necrosis factor alpha; IL-6, interleukin-6; CRP, C-reactive protein.

qualitative changes in HDL. Alcohol increased the lipid content of HDL, augmenting its antiatherogenic effect. In addition, the alcohol-induced phospholipid enrichment of HDL might reduce the inflammatory response of atherogenesis.

HDL has a wide range of properties in the endothelium and is involved in most of the alcohol-related physiological pathways included in this review. HDL is an effective antioxidant, inhibiting the oxidative modification of LDL, reducing its atherogenicity (Barter et al., 2004), and promotes the production of nitric oxide by upregulating eNOS expression (Mineo et al., 2006). The antithrombotic properties of HDL are related to the abilities to attenuate the expression of tissue factor and selectins, to downregulate thrombin generation via the protein C pathway, and to blunt platelet activation (Mineo et al., 2006).

Insulin resistance

Insulin resistance is characterized by an inadequate glucose uptake in peripheral tissues at a given concentration of plasma insulin. It involves an impairment of the nonoxidative (glycolytic) pathways of intracellular glucose metabolism (Ferrannini et al., 1987). As a consequence, there is an increased formation of AGEs, which play a major causative role in hypertension and atherosclerosis through an increase in endothelial dysfunction, inflammatory responses, and increased oxidative stress (Vasdev et al., 2006).

Moderate alcohol consumption has been associated with improved insulin sensitivity in humans (Bell et al., 2000; Lazarus et al., 1997). An analysis of the effect of the intake of various ethanol concentrations in rats showed an inverted U-shaped relationship between alcohol intake and insulin sensitivity (Furuya et al., 2003). Vasdev et al. (2006) hypothesized that by improving insulin resistance, moderate alcohol consumption would limit formation of AGEs and their subsequent hypertensive and atherosclerotic complications. Low ethanol intake may also work to improve insulin resistance by lowering plasma-free fatty acids (Avogaro et al., 2002).

Nitric oxide

Since the classic studies of Furchgott and Zawadzki (1980), it is known that the endothelium produces a substance that is responsible for vasodilation. Later, this substance was characterized as being nitric oxide (Ignarro et al., 1987; Palmer et al., 1987). Nitric oxide and its metabolites have been implicated as clinical markers of endothelial dysfunction (Raitakari and Celermajer, 2000; Vallance and Chan, 2001). Actually, most of the cytotoxicity attributed to nitric oxide is due to peroxynitrite, produced from the reaction between nitric oxide and superoxide (Pacher et al., 2007). Peroxynitrite is implicated in the pathogenesis

of cardiovascular disease (Pacher et al., 2005) and complications of diabetes, including the development and progression of diabetic cardiomyopathy, retinopathy, neuropathy, and nephropathy (Pacher and Szabó, 2006). McKim et al. (2003) showed that the production of peroxynitrite is a mediating factor in alcohol liver injury.

The beneficial effect of low alcohol doses on the cardiovascular system has also been related to the release of nitric oxide (Puddey et al., 2001). Abou-Agag et al. (2005) supported this hypothesis when they found that moderate doses of ethanol increased the expression of eNOS in rats. They suggested that the vascular relaxation resulting from an increase in nitric oxide might explain, at least in part, the cardioprotective benefits of moderate alcohol consumption.

Cortisol

Cortisol is involved in responses to stress and other physiological functions. Mental stress, on the other hand, causes damage to the endothelial function that, chronically, may result in speeding up the atherogenic process (Ghiadoni et al., 2000). It is possible that the association between stress and cardiovascular disease is mediated partly by the relationship between environmental stress and serum cortisol levels (Stephoe et al., 2003). Broadley et al. (2005) investigated whether cortisol is a mediating factor of the effect of stress on endothelial function (evaluated by FMD), and the reduction of baroreceptor reflex sensitivity. For this purpose, the authors submitted two groups of individuals to stress, one of them previously treated with a cortisol synthesis inhibitor (metyrapone) and the other receiving placebo. They found that metyrapone reduced cortisol levels and prevented endothelial dysfunction and reduction of the baroreceptor reflex sensitivity. Sillaber and Henniger (2004) suggested that individuals with dysfunctional responses to stress related to the hypothalamo-hypophyseal-adrenocortical axis could present a greater tendency to alcohol consumption as a stress relief factor. This could be related to the fact that alcohol prevents the stress-induced increases in plasma ACTH and cortisol (Dai et al., 2007). Thus, it is possible that some of the mechanisms of alcohol action on endothelial and vascular function could be mediated by cortisol.

Endothelin

Endothelin, a polypeptide with 21 aminoacids, is one of the most potent endogenous vasoconstrictors ever identified (Levin, 1995; Yanagisawa et al., 1988), producing constriction both in veins and in arteries. Several studies on animal models and humans showed the correlation between endothelin production and activity, and some of the main risk factors for atherosclerosis (Haak et al., 1994). A selective antagonist of one of the endothelin receptors (the

endothelin-A receptor) was able to prevent stress-provoked endothelial dysfunction (Spieker et al., 2002).

The hypothalamo-pituitary axis and endothelin interact in their effects on the vasculature (Broadley et al., 2005). Thus, the activation of the vascular endothelin system appears to depend on cortisol (Broadley et al., 2005) and on other cardiovascular stress markers such as norepinephrine (Touyz and Schiffrin, 2003).

Alcohol consumption raises the endothelin levels in a dose-dependent manner, mediated by increased alcohol-induced oxidative stress (Soardo et al., 2005). The authors showed that blocking oxidative stress prevented the functional changes induced by alcohol in the endothelium. In a subsequent study, the same group of researchers showed that the increase in the endothelin levels could be in the pathway of blood pressure elevation induced by heavy alcohol consumption. This hypertension was rapidly reverted when alcohol consumption ceases (Soardo et al., 2006). Zilkens et al. (2005) also included increased endothelin as a mediator of the effect of alcohol on increased blood pressure.

Adhesion molecules

Another indicator of endothelial dysfunction and an important step in atherogenesis is the expression of the adhesion molecules on the surface of the vascular endothelium in response to lesions (Fries et al., 1993). The intercellular adhesion molecule (ICAM-1) enables the adhesion and transmigration of inflammatory cells to the vascular wall (Ridker et al., 1998). The emission of these molecules in plasma can be considered a marker of atherogenesis and endothelial dysfunction. In patients with angina, but free of flow-limiting lesions, elevated levels of this marker can indicate endothelial dysfunction (Clausell et al., 1999). The dose-dependent elevation of ICAM-1 and selectin-E in alcoholics may reflect the direct or indirect effect of alcohol on the endothelial cell (Sacanella et al., 1999). However, moderate alcohol consumption appears to reduce the expression of these molecules in the endothelium (Sacanella and Estruch, 2003). This information was confirmed in a prospective study when alcohol consumption was shown to be inversely associated with the levels of adhesion molecules (Shai et al., 2006).

Tumor necrosis factor alpha

Badia et al. (2004) analyzed the effect of the moderate consumption of red wine or gin on human monocyte adhesion to endothelial cells in healthy men. Tumor necrosis factor alpha (TNF-alpha)-induced adhesion of monocytes to endothelial cells was virtually abolished after red wine consumption but was only partially reduced after gin consumption. The authors suggested that this effect might be due to the downregulation of adhesion molecules on the monocyte surface.

On the other hand, chronic ethanol-induced damage to various organs has been linked to the increased release of TNF-alpha. In vitro studies demonstrated that the endothelial cell proliferation and re-endothelialization is inhibited by TNF-alpha at the sites of arterial injury (Kishore et al., 2003). Luedemann et al. (2005) showed that the presence of ethanol enhances the TNF-alpha-induced endothelial cell dysfunction. The authors hypothesized that chronic ethanol consumption may negatively influence post angioplasty re-endothelialization, thereby contributing to the development of restenosis.

Interleukin-6

Interleukin-6 (IL-6) may also be among the links connecting alcohol consumption and atherosclerosis (Carty, 1999). It is the main interleukin in the acute inflammatory phase (Baumann and Gaudie, 1994). IL-6 regulates genes that encode most of the proteins involved in this stage (Castell et al., 1990), besides suppressing the hepatic synthesis of albumin (Carty, 1999).

In liver disease caused by alcohol there are elevated concentrations of IL-6 and other interleukins (McClain et al., 1999), while moderate alcohol consumption can inhibit IL-6 synthesis or its actions in hepatocytes (Carty, 1999). In this sense, a prospective study showed an inverse relationship between IL-6 and other inflammatory markers and moderate alcohol consumption (Pai et al., 2006). The authors suggested that these inflammatory markers could constitute the mediating factors of the protective action of moderate alcohol consumption on cardiovascular risk. Maraldi et al. (2006), however, could not confirm this hypothesis. They observed that the alcohol-related decrease in cardiovascular risk was independent of IL-6.

CRP

CRP is a marker of the acute-phase response of the inflammatory process produced by the liver in response to systemic inflammation. It is often elevated in patients with acute ischemia and myocardial infarction (Biasucci et al., 1999). Besides being a predictive factor for myocardial infarction or cerebrovascular accident (Ridker et al., 1997), CRP actively favors atherosclerosis, promoting endothelial activation and macrophage recruitment (Zhong et al., 2006).

The physiological actions of CRP result in a decreased release of nitric oxide and increased expression of IL-6 and IL-8, vascular cellular adhesion of molecules, and ICAM-1 (Zhong et al., 2006). Besides this, the authors also observed that CRP increases the expression of the receptor for AGEs, which is thought to speedup the atherogenesis process.

An evaluation of alcohol consumption over a 12-month period suggested that CRP also shows a U-shaped

association with alcohol consumption (Raum et al., 2006). In this study, the lowest levels of CRP were observed with a consumption of less than 16 g a day. It should be pointed out that the aforementioned study of the effect of alcohol on cardiovascular risk (Maraldi et al., 2006) did not show a mediating effect of CRP on the association between moderate consumption and cardiovascular risk.

Although CRP is influenced by long-term alcohol consumption, drinking in the previous 24 h was not associated with any change in the levels of this marker (Raum et al., 2007).

Hemostatic factors

One of the mechanisms by which moderate alcohol consumption could reduce cardiovascular risk would be by inhibiting platelet reactivity (Belleville, 2002). In this sense, alcohol consumption has been associated with a favorable thrombolytic pattern, protecting against cardiovascular risk (Salem and Laposata, 2005). Moderate alcohol consumption decreases platelet aggregation, increase fibrinolytic activity, and reduce fibrinogen levels (Abou-Agag et al., 2005; Salem and Laposata, 2005). On the other hand, heavy alcohol intake is associated with lower fibrinolytic capacity and a more pro-coagulant state, with a rise in the plasma levels of factor VII, fibrinogen, and viscosity (Lee and Lip, 2003).

The main determining factors of fibrinolysis are the balance between the tissue plasminogen activating factor and the plasminogen activator inhibitor (PAI), both of them derived from the endothelium. Alcohol consumption appears to elevate these two factors (Puddey et al., 2001). It is possible that the amount of alcohol consumed determines whether these modifications would be predominantly associated with improvement or worsening of endothelial function (Puddey et al., 2001). There is evidence that alcohol acts simultaneously to activate and inhibit platelet function. In this sense, ethanol could be a partial platelet-activating factor (Salem and Laposata, 2005), with partial degranulation allowing the continuous circulation of platelets with an altered function.

The Von Willebrand factor, which is synthesized by the endothelial cells, acts on platelet adhesion and aggregation, and an elevated plasma level suggests endothelial damage (Raitakari and Celermajer, 2000). Alcohol consumption in turn appears to lower the levels of the Von Willebrand factor (Kumari et al., 2000).

A review of the antiatherogenic potential of red wine suggested the existence of an additional benefit (besides alcohol itself) of the phenolic components of red wine over the processes involved in the beginning, progression, and breakdown of atherosclerotic plaques (Szmitko and Verma, 2005). Moderate alcohol consumers could have lower fibrinogen levels, Von Willebrand factor, and factor VII as already mentioned. On the other hand, wine consumers would also have a reduction in the levels of the antigen that

inhibits the plasminogen activator (PAI-1-Ag), leading to a reduction in hemostasis (Szmitko and Verma, 2005).

Gender and ethnic differences

Most studies on the effects of ethanol on endothelial function were conducted in men in Western populations. However, alcohol consumption is very common among women, and nearly one-third of the alcohol-dependent individuals in the United States and Australia are women (Teesson et al., 2006). Studies of women with alcohol dependence in treatment suggest that they often experience greater physiological impairment earlier in their drinking careers (Hommel et al., 2001). Among the reasons for such susceptibility is the lower total body water content of women in comparison to men (Mumenthaler et al., 1999) and a diminished activity of alcohol dehydrogenase, the primary enzyme involved in the metabolism of alcohol (Chrostek et al., 2003). Part of these differences in the response to alcohol in women could be related to endothelial function. Rajasingh et al. (2007) reported the occurrence of endothelial cell dysfunction in alcohol-consuming female rodents, suggesting that ethanol blunts the beneficial effects of estrogen on endothelial cells. However, despite these gender differences, a study designed to compare the associations of drinking frequency and quantity with risk of myocardial infarction in men and women showed similar beneficial effects of moderate drinking in both genders (Mukamal et al., 2005).

Considering possible interactions between genetic factors and alcohol consumption on cardiovascular risk (Hines et al., 2001; Younis et al., 2005), ethnicity should also be considered when analyzing the effects of alcohol on cardiovascular health. There are significant genetic differences in ethanol metabolism between Western and Asian populations, where approximately 50% of Orientals lack the activity of the mitochondrial low-K_m aldehyde dehydrogenase and present a flushing reaction after drinking that decrease their risk for alcohol dependence (Yin, 1994). There is evidence that blood pressure and HDL cholesterol are more prone to be affected by drinking in flushers than in non-flushers, at least in patients with diabetes (Wakabayashi and Masuda, 2006).

There are also reports on differences between African-derived and European-derived individuals regarding the effects of alcohol on blood pressure. Steffens et al. (2006) verified that non-white individuals who consumed large daily amounts of ethanol (30 g or more for men or 15 g or more for women) were at higher risk of developing hypertension, replicating similar findings from the “Atherosclerosis Risk in Communities Study” cohort for individuals with an African ancestry (Fuchs et al., 2004). The effect would be protective for whites and harmful for blacks. Furthermore, the protective effect appeared to be more intense among whites who rarely consumed alcohol.

These data suggest the possibility that part of the beneficial effects of alcohol could actually be due to a bias related to the life style of the alcoholic beverage users. Among the possible confounding factors are physical activity and the psychosocial profile. A recent review of data on the putative cardioprotective effect of alcohol concluded that a real association between the consumption of alcoholic beverages and the incidence of coronary artery disease has not yet been unveiled (Fuchs and Chambless).

Taken together, it is possible to infer that gender, ethnicity, lifestyle, and genetic polymorphisms might impact the associations between alcohol consumption and cardiovascular risk. These pharmacogenomic and environmental heterogeneity issues clearly deserve further investigation.

Conclusions

Alcohol has dose-dependent and dual effects on several physiological functions, being associated with beneficial and harmful vascular effects. It is difficult to establish the precise sequence of events involved in the action of alcohol on the vascular endothelium at the current stage of research. However, it is possible to infer a pattern in which the first steps following alcohol consumption involve influences in insulin resistance, lipoproteins, oxidative stress, and production of AGEs. The action of these factors in the vascular endothelium may then influence the levels of several markers related to the J-shaped curve.

This huge volume of evidences has generated a broad discussion on the medical attitude toward the consumption of alcoholic beverages. The truth is that data are not yet sufficient to support the prescription of moderate alcohol consumption (or specifically, red wine) to abstemious patients. First of all, so far it has been impossible to totally exclude life style related biases, gender, and ethnic effects and individual genetic variability that might confound the associations observed between alcohol consumption and cardiovascular risk. Furthermore, large long-term, randomized clinical trials would be needed to evaluate the effects of alcohol. However, the ethical aspects of these studies are doubtful, considering the serious negative consequences of alcohol use (Szmitko and Verma, 2005). In view of this limitation, it will still be necessary to rely on the results of prospective controlled observational studies and laboratory studies on mechanisms of action of ethanol to confirm if it is really helpful for cardiovascular health. Considering the addictive potential of alcohol, the identification of substances that mimic only its beneficial effects is warranted.

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