For much of the last century, a major medical interest in ethanol research has been related to the biological effects of ethanol abuse on the brain, liver, and heart. Focused in urban centers where addiction to this agent was a common phenomenon, little consideration of the dose-response relationship at the lower end of the scale was provided. Fortunately, there has been a growing interest in this relation over the past 2 to 3 decades.

Epidemiological investigation relying on individual histories of daily intake found that an alcohol intake of 3 to 5 drinks per day was associated with a diminished incidence of myocardial infarction as well as total mortality.\(^ {1a}\) The frequent association with some degree of hypertension was apparently of insufficient impact to affect this beneficial outcome. Most data suggested that this advantage was most evident in those older than 50 years, with some sex differences.

Subsequently, a long-term study from an oncology center pointed out the increased risk of certain cancers associated with alcohol use, independent of tobacco use.\(^ {1b}\) The threshold for an increased appearance of cancer was at the moderate level of 3 to 4 drinks per day in men.\(^ {1b}\) In women, the increased risk for breast cancer seemed to have a threshold of 2 drinks per day.\(^ {2}\) The term “light drinking” has been used to indicate a level not exceeding 12 to 15 g (1 drink) of ethanol per day.

Major contributions to this field have been made by the Physicians Health Study, which originally observed the cardiovascular benefits of the higher threshold in men. More recently, this group has indicated that no further benefit may be achieved above 2 drinks per day.\(^ {2}\) The term “light drinking” has been used to indicate a level not exceeding 12 to 15 g (1 drink) of ethanol per day. The association between alcohol and risk of other causes of death, the study of physicians should diminish, although not eliminate, uncertainties about the nondrinking controls. Self-reporting seemed to be a reliable method for the general classification of drinking habits in this group. Although alcohol consumption was measured at one point in time, subsequent measurements after 8 years were similar.

The association between stroke and alcohol consumption, corrected for the relevant variables, has also been analyzed. About 50% of subjects were using low-dose aspirin; therefore, the absolute effect of ethanol per se is unclear.\(^ {3}\) The association between alcohol intake and total stroke incidence revealed a risk reduction of \(\approx 20\%\) after adjustment for important confounders. The benefit was observed among physicians who had only 1 drink of alcohol per week, and the magnitude of this protective effect did not increase with greater consumption.

In view of the prior observation that light to moderate ethanol intake has an advantage that is most evident in those with cardiovascular disease, recent observations on the prevalence of cardiac disease in diabetics have been of great interest. Investigations of adult-onset diabetic patients at the Wisconsin Epidemiologic Study of Diabetic Retinopathy have shown a reduction of coronary heart disease mortality with low doses of ethanol over a 12-year follow-up in which both sexes were represented.\(^ {5}\) Although the zero-intake controls seemed to exhibit more confounding risk factors, the benefit persisted after statistical corrections. The apparent lack of influence of light to moderate drinking on the regulation of blood glucose was noteworthy. A significant benefit was observed at 1 drink per week. In contrast to the recent Physicians Health reports,\(^ {2,3}\) an additional advantage seemed to exist at the level of 1 drink per day.

The article by Solomon et al\(^ {6}\) in the current issue of Circulation describes this relationship in the Nurses Health Study in Boston. This study had a follow-up of 14 years and...
a convincing correction for associated risk factors. No deterioration of metabolic control occurred in these subjects versus nurses with zero intake, which is noteworthy in view of the known effects of higher doses on pancreatic function. At an average of less than half a drink of alcohol daily, the risk ratio was 0.72 on multivariate analysis. The subset consuming ≥5 g daily (2 to 3 drinks per week) had a risk ratio of 0.45. Thus, this study and that of Valmadrid et al. in contrast to examinations of nondiabetics, showed an apparent gradient effect in the low-dose range.

Regarding potential mechanisms for a reduction of cardiovascular events, an increase in high-density lipoprotein cholesterol has been documented in drinkers, but this increase was not evident at lower doses of ethanol. The effects of alcohol on thrombosis and nitrous oxide metabolism and their potential relation with the prevention of cardiovascular disease are controversial. A recent examination of carotid atherosclerosis by ultrasound found no significant difference in wall thickness between patients with moderate drinking habits and controls. Moreover, the apparent protective effect of a single drink per week implies that other mechanisms may be involved. An issue yet to be resolved is the influence of non-alcohol-containing beverages and plant foods, which may contain putative cardioprotective substances present in some alcohol drinks, in these populations.

In view of the lack of a known mechanism for the effects of ethanol in low doses, a potential mode of action related to diabetes is considered in the study by Solomon et al. A mechanism specifically related to diabetes has been suggested as a result of investigations in animal models and humans, in which advanced glycation end products related to collagen have been observed in the arterial system and left ventricle. Acetaldehyde, which is derived from ethanol oxidation, can react with nucelophiles to form covalent addition products. The interaction of acetaldehyde with early glycation products in vitro produces a stable complex that prevents the progression of the formation of advanced glycation end products.

When ethanol was administered to diabetic rats for 4 weeks to produce the aldehyde increments, a significant decrease in red-cell advanced glycation end products was observed compared with untreated diabetic rats, without an effect on hyperglycemia. Although the in vitro assays were performed at very high acetaldehyde levels, the animal study suggests the potential for an in vivo effect. However, a quantitative relationship with ethanol intake and generation of the aldehyde is not known.

Alternatively, acetaldehyde may react with lysine residues to form stable collagen adducts. In a canine model fed 36% of calories as ethanol for 6 months, collagen-linked adducts were increased in heart muscle, consistent with acetaldehyde binding to the protein. Thus, the net effect in tissue will depend on the relative dominance of these two processes. Whether early glycation products are sequestered in diabetics or significant irreversible adducts are found after low doses of ethanol must be examined.

No data exist on the relative merits of optimal control of glucose in diabetes and ethanol use. Clearly, the elimination or modification of conventional cardiovascular risk factors is essential. The patient who is abstinent or using light to moderate amounts of alcohol should discuss the risks and benefits of alcohol consumption with a physician and base the use of alcohol on his or her personal situation. The surprising feature of these recent investigations is the reported efficacy of <1 drink per day. However, the subject who has been abstinent may find that tolerance to alcohol may create, in time, a need for a larger intake up to the range where unhealthy effects can result.

References


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