ISSUES IN MEDICINE

Alcohol – foe or friend?

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In the same month that this manuscript was prepared, newspapers had twice warned the public about the negative aspects of alcohol consumption. South African drinkers consume among the highest volumes of alcoholic beverages in the world, at approximately 50 ml ethanol per drinker per day,[1] making alcohol abuse one of South Africa's top ten health and social problems. Alcohol abuse is clearly associated with many adverse health effects. In South Africa, fetal alcohol syndrome (FAS) is of particular concern since the highest prevalence of FAS in the world occurs in the Western Cape.[2]

While it is generally accepted that moderate, responsible consumption of alcoholic beverages is not harmful, evidence is emerging that there may even be health benefits. Moderate drinking is now generally accepted as 10 - 35 g alcohol per day. Evidence for the beneficial effects of the consumption of alcoholic beverages on health may be derived from epidemiological or experimental research. In the absence of a controlled interventional study there should be strong evidence from both avenues of investigation, and the benefits should exceed the harm before public health recommendations can be made to include the consumption of alcoholic beverages in daily living. The purpose of this review is to provide some background information on alcoholic beverages in general, but with an emphasis on wine, and to describe the potential health benefits of consuming alcoholic beverages.

Alcoholic beverages

Studies examining the impact of alcoholic beverages on health report the intake variably as units or grams of alcohol, representing almost pure ethanol (ethyl alcohol), per day. A unit of alcohol is defined as approximately 10 g ethanol, which is equivalent to 1 drink (100 ml wine, 200 ml beer, 50 ml fortified wine and 25 ml spirits). The fermentation process that yields wine and beer is limited by the sugar content and the alcohol concentration, since the latter will eventually inhibit fermentation. Spirits have higher alcohol concentration because of distillation. The 'proof' is a measure of the alcohol concentration of alcoholic beverages, being twice the percentage of alcohol by volume. Sherry and port are 'fortified' by additional alcohol.

Wine essentially comprises water, ethanol, organic acids, aldehydes, ketones, esters and many different phenolic compounds that contain at least one hydroxyl group bound to an aromatic ring. Red wines contain approximately 1 mg/ml of phenols, about 5 - 10-fold more than white wines. Approximately half of the total extractable phenols in grape berries enter red wine. Fig. 1 shows the distribution of these compounds in the grape berry.

The bioavailability of the different phenolic compounds varies widely. After the consumption of 10 - 100 mg of a single phenolic compound, the maximum plasma concentration is still less than 1 μmol/l, and urinary excretion varies from 0.3% to 43% of the ingested mass of phenols, depending on the particular phenol. The kinetics and plasma absorption of at least 18 major polyphenols has been studied, but not linked with health status.[3]

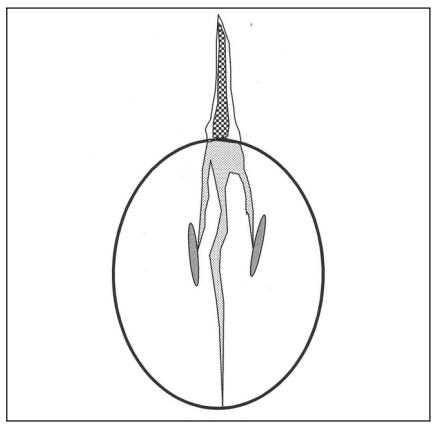

Fig. 1. Diagram of a grape berry showing the distribution of phenols.

Wine polyphenols may broadly be divided into non-flavonoids and flavonoids, with the latter making up the larger group. Some of the individual chemical structures are depicted in Fig. 2. Non-flavonoids include several classes such as the hydroxycinnamic acids, the hydroxybenzoic acids and the stilbenes, of which resveratrol is the best-characterised. Flavonoids are organic molecules containing 15 carbon atoms and 2 benzene rings (A and B). They may be classified into the major classes, viz. flavanols, flavonols and anthocyanins. Flavanols form the largest class and include monomeric

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catechins and oligomeric and polymeric proanthocyanidins. Procyanidins are oligomers of catechin and epicatechin. The main simple flavonols are quercetin, kaempferol and myricetin.

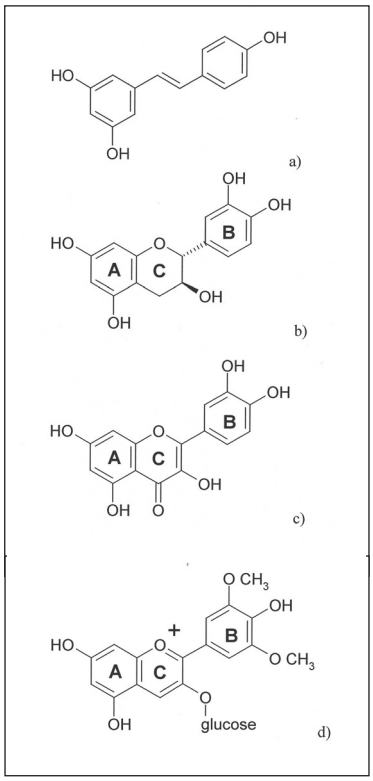

Fig. 2. Chemical structures of a) resveratrol, b) (+)-catechin, c) quercetin and d) malvidin-3-glucoside (an anthocyanin).

The pharmacokinetics of alcohol metabolism have been studied extensively. Alcohol dehydrogenase (ADH) reversibly oxidises primary and secondary alcohols to their corresponding aldehydes and ketones, much of which takes place in the liver. Aldehyde dehydrogenase oxidises the potentially reactive aldehydes to acetate which, once conjugated to acetyl CoA, enters intermediary metabolism. Genetic variations in ADH are known to influence alcohol metabolism.[4]

Epidemiological evidence

In 1926 the first finding of a U-shaped association between all-cause mortality and the consumption of alcoholic beverages was reported by Raymond Pearl in a book titled *Alcohol and Longevity*.[5] Subsequently, a large number of epidemiological studies also demonstrated this U- or J-shaped association, indicating that moderate daily alcohol consumption results in a significant reduction in mortality compared with abstinence or excessive consumption. In the 1970s, when this apparent benefit was confirmed,[6] little attention was paid to these results. It was not until the 1980s that the idea that moderate consumption of alcohol might be beneficial to health led to more systematic research. Epidemiological studies have shown various benefits of moderate alcoholic beverage consumption, with the vast majority of research results concerning the benefits to vascular disease, in particular coronary heart disease (CHD).[7,8] Reports indicate a reduction of 30 - 50% in vascular deaths. The 'French Paradox', a sometimes controversial phenomenon described in 1992 by Renaud and de Lorgeril,[9] indicated a lower rate of mortality from CHD among the French compared with other developed countries, despite similar dietary intakes in these countries. The putative explanation was that the higher consumption of red wine protected the French against heart disease. It has been suggested, however, that the paradox may be due to differences in data collection.

Compared with abstention, moderate consumption of alcohol, particularly wine, is associated with better cognitive function and memory in subjects older than 65 years, and higher bone mineral density among postmenopausal women.[10,11] Interestingly, moderate consumption of alcohol has been reported to diminish the incidence of type 2 diabetes mellitus[12] and to reduce cardiovascular disease (CVD) in established diabetic men and women.[13,14] Various studies have reported a reduction in the risk for total and ischaemic strokes,[15] but an increased risk of haemorrhagic stroke[16] in regular consumers of alcoholic beverages relative to abstainers or occasional drinkers. The cumulative epidemiological evidence summarised in Fig. 3 shows paradoxical results – heavy drinkers suffer predominantly harmful results while abstainers may fare less well than regular moderate drinkers in the risk for CHD, stroke and total mortality.

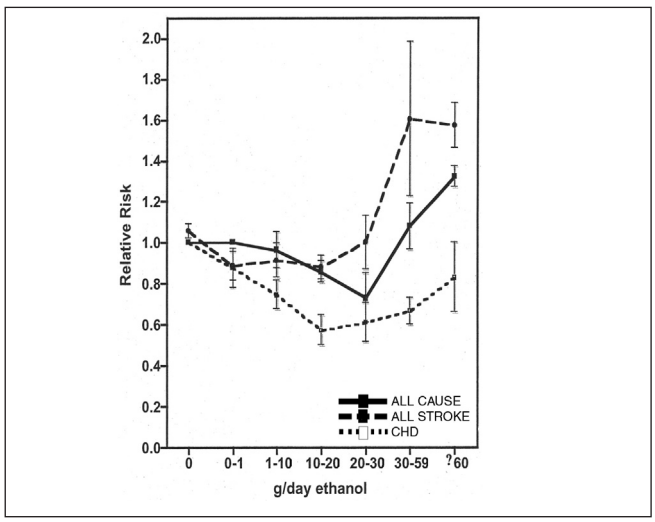

Fig. 3. All-cause mortality, all-stroke and CHD risk in relation to alcohol consumption. Data reflect the means and standard error of the mean (SEM) from 7 all-cause, 11 all-stroke and 11 CHD studies, respectively.

While epidemiological studies may associate alcoholic beverage consumption with better health, it is difficult to prove a causal relationship for several reasons. If a randomised interventional study is not undertaken there may be a selection bias for subjects who drink alcoholic beverages or even a particular kind of alcoholic beverage. Because different diets are often associated with the consumption of different alcoholic beverages, it may be difficult to attribute the benefit to the beverage. Wine consumption, for example, tends to be associated with a higher intake of healthy food such as fruit, vegetables, fish and olive oil. Additionally, in communities with higher alcohol consumption, alcohol-related diseases may be the reason for abstention. Furthermore, studies rely on self-reported drinking, which may be underreported. Factors such as gender, age, diet, smoking, economic status, social class, ethnicity and education play a role in population health and may therefore also be confounders in studies of the effects of alcoholic beverages on health. Epidemiological studies should ideally be carried out over a number of years because diseases against which alcoholic beverages may confer protection, e.g. CVD, develop slowly. Similarly, harmful effects may only be evident in the long term. The changes in the body or health outcomes that are being studied may require large sample numbers to demonstrate an effect.

Many reports support the proposal that wine has superior effects on health relative to other alcoholic beverages.[7,17,18] Some studies have found that all alcoholic beverages have a positive effect on the risk of CHD and mortality. Wine drinkers have been found to have higher IQs, to smoke less, to exercise more, to be better educated and to have higher socioeconomic status than beer and spirit drinkers.[19] The interpretation of reported differences in health benefits of the different alcoholic beverages should be viewed with caution until confounding effects have been clearly ruled out or mechanistic differences are evident. Although the balance of epidemiological evidence is in favour of moderate consumption of alcoholic beverages being conducive to good health, the central questions are still largely unanswered. It will be difficult to resolve the different contributions of alcohol and phenols to health, whether wine is superior to other alcoholic beverages or whether red wine is superior to white wine, without resorting to interventional studies or experimental evidence.

The preceding discussion concerned favourable outcomes, but some studies have failed to demonstrate any effect and other studies have demonstrated detrimental effects. Data for the effects of moderate alcohol consumption on cancer are inconclusive, with some studies finding an increased risk of cancers of the liver[20] and upper digestive tract,[21] particularly after consumption of beer and spirits, and an increased risk of breast cancer.[22] Other studies[20,23] found no increased risk of breast, lung, bladder, prostate or ovarian cancers. A number of epidemiological studies indicated an association between alcohol consumption and increased blood pressure, with a threshold dose of 20 - 30 g ethanol per day, above which the pressure increases unequivocally. The acute and chronic effects of excessive alcohol consumption on social and physical wellbeing are well established although precise mechanisms are not known.

Experimental evidence

The influence on health of the ethanol in alcoholic beverages has not been fully established and reports are contradictory. Some studies have reported that it is the ethanol that is responsible for the beneficial health effects rather than the other characteristics of the beverage.[24,25] This is contradicted by other studies which demonstrate that the benefits of wine in particular are derived from the non-alcoholic fraction, suggesting that phenols and/or antioxidant activity confer(s) the benefits.[26,27] Red wine is often reported as having greater antioxidant activity that can be attributed to its higher phenolic content. However, some white wines that have an increased extraction of grape skin polyphenols, have similar antioxidant characteristics to red wines.[28] An increase in the expression of endothelial nitric oxide synthase (eNOS), an enzyme that increases the production of NO, thereby enhancing vasodilation, is associated with red wine but not with ethanol. Ethanol-free red wine extracts have also been shown to improve post-ischaemic ventricular function[29] as well as to inhibit *ex vivo* low-density lipoprotein (LDL) oxidation.[30] Other studies suggest that both the polyphenols and the alcohol in red wine reduce the incidence of CHD, but by different mechanisms.

Several additional potentially favourable effects of alcoholic beverages are known. By preconditioning the heart, chronic low-dose consumption of ethanol was found to maintain rat hearts in a protected state; when ischaemia occurred, damage measured by infarct size was reduced.[31] Red and white wine have been found to improve endothelial function in human volunteers.[32] High-density lipoprotein (HDL) concentrations are significantly and consistently increased in humans after consumption of alcoholic beverages, particularly red wine.[33,34] Platelet aggregation promotes the development of atherosclerosis by the formation of blood clots in arteries. A number of studies[35-37] have demonstrated the anti-aggregating effect on platelets of alcohol, red wine and dealcoholised red wine. Moderate consumption of red wine has been found to lower homocysteine concentrations in obese adults who have an increased risk of vascular morbidity and mortality.[38] Red wine has bactericidal effects against *Helicobacter pylori* (associated with gastric cancer) and *Chlamydia pneumoniae* (which is associated with the development of CHD).[39,40] Although not as effective, consumption of beer and spirits also has this effect.[41] Red wine has been found to inhibit growth of various cancer cell lines such as breast, prostate and colorectal

cancer.[42-44] A recent finding[45] suggests that resveratrol influenced cell senescence favourably by mimicking the calorie-restriction action of proteins called sirtuins. Congeners that are more stable than resveratrol are being sought for further study.

Conclusions

Atherosclerosis is the dominant cause of morbidity and mortality in developed countries and is rapidly rising in developing countries.[46] It is preferable to combat atherosclerosis by means of preventive strategies involving lifestyle modification, including a balanced diet, exercise, maintaining an ideal body weight, and no smoking. Epidemiological evidence suggests that moderate consumption (1 - 3 drinks per day) of alcoholic beverages, particularly red wine, is associated with an overall improvement in health, especially cardiovascular health. Although the epidemiological information is attractive, it is not adequately compelling for the deliberate inclusion of alcoholic beverages in the lifestyle of westernised subjects. Nevertheless, moderate consumption of affordable alcoholic beverages in otherwise healthy subjects will not increase the risk for disease, especially if it accompanies a healthy lifestyle. The consumption of larger amounts of alcohol is clearly ill-advised, and the consumption of alcoholic beverages during pregnancy clearly places the fetus at risk for developmental abnormalities.

Although several lines of experimental evidence suggest mechanisms by which alcoholic beverages may reduce the risk of vascular disease, there is inadequate understanding of atherogenesis to know whether these mechanisms apply to any given individual at risk and whether the alcoholic beverage will be of direct benefit. Scientific research will hopefully elucidate these mechanisms for specific intervention. Research into the health benefits of alcoholic beverages may therefore yield new avenues of treatment for atherosclerosis in the future.

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