Meeting the needs of Mediterranean nations: Mediterranean diet and the area's specific diseases

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Alcohol abuse

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ABSTRACT

Chronic alcohol consumption is a world-wide socio-economic problem. Three metabolic pathways of ethanol were describe in human - alcohol dehydrogenase (ADH), microsomal ethanol oxidizing system (MEOS, CYP2E1) and catalase. Ethanol directly bounds to different molecules (e.g. etylglucuronid) and ethanol per se and its metabolites have toxic effect on biological stuctures.

Alcohol abuse is well known for its liver diseases e.g. cirrhosis (the most frequent cause in Europe and US) and hepatocellular carcinoma.

Chronic alcohol consumption leads to cardiovascular diseases (e.g. hypertension, cardiomyopathy), pancreas damage, myopathies, osteoporosis, neurological and psychiatry diseases including fetal alcohol syndrome and addiction.

Alcohol comsumption may lead to cancer via several mechanisms, per se (solvent for carcinogens) and its metabolites. Acetaldehyde, a cancerogen, has mutagenic effect on DNA, oxidation of ethanol produces the reactive oxygen and nitrogen species with different effects e.g. cell transformation, DNA, protein and lipid damage. The changes of folate metabolism, altered methylation of DNA, reduction of retionic acid influences on cancer development.

The high rate of alcohol consumption has become a great social-health problem. Consumption of alcohol is still increasing in many countries, but in some countries is stable or decreasing (e.g. Mediterranean region). The data across Europe shows that 10% of all cancers in men and 3% of all cancers in women can be attributed to alcohol consumption. Australian data suggests that alcohol intake accounts for 5% of the total cancer burden of disease. Alcohol consumption is one of the leading causes of mortality and morbidity in many developed countries.

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Alcohol has been consumed by people since the dawn of mankind. Beer was commonly produced already in ancient Egypt and wine has been known for millennia. However, excessive alcohol consumption has been mainly attributed to the second half of the twentieth century. Alcohol is a very dangerous cytotoxic substance damaging the organism both acutely and chronically; what is even more dangerous is that it causes addiction. Any alcoholic beverage in any quantity is potentially harmful to human health.

Alcohol-induced damage to the organism derives from its direct effect, in particular its metabolism and the substances produced thereof. The direct effect manifests itself mainly in changes to biological membranes and influencing their fluidity, potentially also by intercellular interactions with the possible alcohol-induced malnutrition caused by its effect on the epithelium of the small intestine.

There are four metabolic pathways of ethanol in the human organism:

1) alcohol dehydrogenase (ADH);
2) microsomal ethanol oxidizing system (MEOS, CYP2E1);
3) catalase, and
4) non-oxidative metabolism.

These enzyme systems can remove 90–98 percentage of alcohol from the human body; the unchanged residual amount is excreted from the body through breath, sweat and urine.

The main enzyme in ethanol metabolism belongs to the cytosolic dimeric alcohol dehydrogenase (ADH, E.C. 1.1.1.1) which catalyses the conversion of ethanol to acetaldehyde, which is carcinogenic. In addition to oxidation of alcohols, it also contributes to the metabolism of steroids and omega-oxidation of fatty acids. Oxidation of ethanol in the digestive tract can reduce the systemic ethanol concentration by up to 20%. ADH is developmentally and gender conditioned, resulting in lower ADH activity in females. In addition, this enzyme is not inducible and its rate is limited not only by NAD^+ and oxidises in 92–96% of the alcohol ingested.

The emerging acetaldehyde is further metabolised by aldehyde dehydrogenase (AlDH, E.C.1.2.1.3.) into the end product acetate, which can be involved in a number of metabolic processes within the organism. AlDH can be identified in almost all organs, with high activity in the liver and in tissues that are in direct contact with the ambient environment. In a large portion of the Asian population, the genetic polymorphism ALDH2*2 is described, which results in an increase in acetaldehyde due to the lower activity of AlDH; there is also a higher incidence of tumour growth in this population.

Oxidation of alcohol to acetaldehyde and subsequently to acetate requires reduced nicotine cofactors, which alter the ratio of reduced and oxidized NAD, thereby altering the redox cell environment. These changes result in increased lactate and ketone body formation and reduced gluconeogenesis and Krebs cycle activity, followed by increasing of acetate for lipid synthesis. Acetaldehyde is a very reactive compound binding itself to nucleic acids, phospholipids and, above all, to proteins, including albumin,

collagen and haemoglobin, thus altering their structure and function. Nucleic acid modifications, the formation of etheno-DNA adducts, are one of the possible mechanisms of carcinogenicity of alcohol, including inhibition of DNA repair.

Microsomal ethanol oxidizing system (MEOS, cytochrome P450IIE1 or CYP2E1), is an inducible ethanol oxidizing system that metabolizes xenobiotics and many other substances including vitamin D. Induced CYP2E1 can activate carcinogens and hepatotoxins by converting them into even more toxic metabolites. Among the by-products of ethanol oxidation, there is the increased formation of reactive oxygen species, changes in human antioxidant protection systems, and the development of oxidative stress, which has many pathobiochemical effects on the organism (1,2,3,4).

Alcohol consumption is associated with more than 200 diseases (5), including a number of tumours, hypertension (6), liver cirrhosis (7), brain damage and diabetes (8). Ethanol abuse also damages the pancreas (causes up to 50% of chronic pancreatitis), the nervous system (psychiatric diseases, addiction treatment) and the muscles; it affects the immune system, the nourishment of the organism; and contributes to the formation of osteoporosis. Drinking alcohol during pregnancy may cause fetal alcohol syndrome with an incidence of 3.7 per 1000 live births in Europe (9). Children and pre-adolescents (people under 18 years of age) who consume alcohol are at an increased risk of alcohol-induced damage to the organism (10), including the risk of alcohol dependence.

Alcohol is most commonly associated with liver damage. Alcohol-induced liver damage includes a variety of nosological units, such as steatosis, alcoholic hepatitis, cirrhosis, and hepatocellular carcinoma. In Europe and the US, alcohol is the most common cause of liver cirrhosis. According to the GDB (Global Burden of Disease) study, roughly half of the cirrhosis deaths were caused by alcoholic liver cirrhosis. The basic mechanisms of hepatic tissue damage include centrilobular hypoxia, neutrophil infiltration and immune response activation (IL-8 activation, leukotriene B4, inflammatory cell infiltration), cytokine and endotoxin exposure, antigen adduct formation, and oxidative stress damage (7).

The influence of ethanol on the cardiovascular system is very much debated in terms of its cardioprotective effects at very small doses (20 g/day). The protective mechanism is enabled by an increase in HDL-cholesterol, ApoA I, paraoxonase activity and adiponectin through lowering LDL-cholesterol; by an antithrombotic effect; and by an increase in insulin receptor sensitivity (11). In a recent study (12), the authors have processed data from 83 studies on 59,912 participants, deriving interesting conclusions. When evaluating a total of 40,310 deaths, it was found that the risk rose from 100 g of ethanol per week. In the study of deaths for cardiovascular disease (39,018), there was a decrease in the risk of death in people consuming 100–200g of ethanol per week. When analysing these overall data, the decrease was observed only in myocardial infarction. The above-mentioned paper states that a person aged forty who consumes more than 350 g of ethanol per week will shorten his life by four to five years. Consuming higher doses of alcohol means a higher risk of heart attack, atrial fibrillation and also hypertension (approx. 10% of hypertension is estimated to be caused by alcohol consumption) and cardiomyopathy (11).

Chronic alcohol consumption is associated with 10 % of tumours in males and 3% in females. It is considered a risk factor in upper gastrointestinal tract tumours (UADT – oral cavity, pharynx, larynx, and oesophagus), hepatocellular carcinoma, colorectal carcinoma and breast cancer (13, 14). The impact of alcohol abuse on the risk of lung and pancreatic carcinoma is also discussed.

As for the UADT tumours, 25–68% of them are associated with alcohol consumption with the risk increasing significantly in smokers. The risk of developing the tumour is significantly higher – twice to six times – when consuming 50–100 g/day (13). The threshold risk value for colorectal cancer is 20 g of ethanol a day (15). The incidence of hepatocellular carcinoma increases and alcohol is the major risk factor in Europe and the US. There are a number of mechanisms leading to tumour growth – high dose of alcohol, increased oxidative stress, formation of modified DNA bases, DNA repair disorder, increased acetaldehyde, folic acid deficiency (methylation disorder), inflammatory reactions, changes in iron metabolism, increased estrogen, decreased levels of retinoic acid (hyperregeneration and hyperproliferation), risk allelic variants of alcohol metabolising genes (ALDH2*2, ADH1B*2, ADH1C*1) leading to increased acetaldehyde concentration (16,17), coincidence with precancerous condition (gastroesophageal reflux disease, colon polyps, colitis) or other diseases (e.g. hepatitis, NASH, hemochromatosis).

According to WHO data, alcohol consumption declined in Europe between 1990 and 2014, contrary to East Asia, South America and Africa, where there was an increase in consumption. A significant drop in consumption occurred in the Mediterranean countries – Italy, Spain, France, Greece (18, 19). The European Union estimates the damages caused by consumption of alcoholic beverages at 125 billion EUR per year. In the EU countries, 195 000 people on average die of alcohol-related injuries, liver disease, tumours, etc. every year. It is worth pointing out that in the European Union, every seventh death (14 %) in males and every thirteenth (7 %) in females aged 15–64 are related to alcohol consumption, which means about 95 000 males and 25 000 females per year (12 % of all deaths). It is the third most common cause of early deaths and illnesses in the EU, following smoking and high blood pressure related diseases. Alcohol is linked to the deaths of young people (15–29 years) at 5% globally, 25% in Europe and, unfortunately, 33 % in Eastern Europe. Around 55 million adults in Europe are at risk of alcohol addiction (consuming more than 40 g/day) (20).

Alcohol as a chemical molecule has been accompanying mankind for several millennia. Current data and meta-analysis of studies suggest that consumption of 100–200 g of ethanol per week can be tolerated (not recommended) on condition that there is a two-day gap between consumption. Alcohol-induced damages are important from both the health and the social point of view (psycho-social and economic consequences).

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