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Effects of Ethanol Consumption on Different Organs-A Brief Overview

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Abstract: Effects of ethanol consumption on different organs are discussed in this review. Chronic alcoholism is a major public health problem and causes multiorgan diseases and toxicity. Ethanol is the most psychoactive substance used in the society. This is a small molecule soluble in both water and lipids. Therefore it permeates all tissues of the body and affects the vital functions. It is causally related to more than 60 medical conditions. Therefore a systematic effort is required to enhance the defense of the body against the toxic effects of ethanol consumption considering the nutritional uptake of an individual. The blood stream transports ethanol to all parts of the body, so most tissues such as brain, liver, kidney and testes are exposed to the same concentration as in blood.

Key words: Alcohol, brain, kidney, liver, testes

INTRODUCTION

Alcoholic beverages have been used in human societies since the beginning of recorded history. The patterns of alcohol intake around the world are constantly evolving and alcohol is ubiquitous today (Das *et al*., 2006). In recent times alcoholism has become a perennial and pervasive problem gradually among people (Marshall and Murray, 1992; Das *et al*., 2006). There is thus a strong justification for the health profession to step up its advocacy creating awareness of alcohol consumption. Ethanol is a small molecule soluble in both water and lipids. Therefore it permeates all tissues of the body and affects the vital functions. Alcohol related medical disorders virtually affect almost all organs of the body (Anderson, 1993; Das *et al*., 2005). Excessive alcohol intake leads to a variety of gastrointestinal, neurologic, cardiovascular and malignant diseases (Das *et al*., 2006). So in this study we elucidated the role of ethanol consumption on different organs.

EPIDEMIOLOGY

Alcohol abuse can be found among all age groups, predominant in men. Notable ethnic differences observed were in the prevalence of alcohol-induced liver disease and associated mortality. Overall consumption or the average volume of alcohol consumption or the average volume of alcohol consumed has been the usual measure of exposure linking alcohol to disease in recent decades. The average volume of consumption works as a risk factor mainly through biological and biochemical effects, including dependence, to produce long-term health consequences (Mandayam *et al*., 2004; Bellentani *et al*., 1997; Das *et al*., 2006).

The volume of consumption as well as the patterns of drinking, especially irregular heavy drinking has been shown to determine the burden of disease. In other words, the impact of the average volume of consumption on mortality or morbidity is partly moderated by the way alcohol is consumed by the

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individual (Room and Makela, 2000). Patterns of drinking have been linked not only to acute health outcomes such as injuries, but also to chronic diseases such as Coronary Heart Disease (CHD) and sudden cardiac death (McKee and Britton, 1998).

There is general agreement that excessive alcohol consumption is associated with an increased risk of cirrhosis. However, there is no consensus on the exact dose or a specific dose-response relationship for cirrhosis. Evidence suggests that there is an increased risk with ingestion > 60-80 g day^{-1} of alcohol in men and > 20 g day^{-1} in women. However, 6-41% of those drinking these amounts will develop cirrhosis. Evidence suggests that even in patients with an extremely high daily alcohol intake (> 120 g day^{-1}), only 13.5% developed alcohol- induced liver damage (Bellentani *et al*., 1997). It is believed that other factors such as genetic susceptibility and dietary intolerance may be co-factors in alcohol-induced damage.

The blood stream transports ethanol to all parts of the body, so most tissues are exposed to the same concentration as in blood (Norberg *et al*., 2003; Patton, 1994).

SMALL INTESTINE

Alcohol consumption decreases the absorption of a number of nutrients and can alter their storage, metabolism and excretion. Further, it affects the metabolism and storage of fat-soluble vitamins and also causes deficiency of many water-soluble vitamins. Decrease of many antioxidant levels also occur in the body due to alcohol consumption. The absorption of several nutrients, vitamins and other elements is disturbed due to chronic alcohol consumption (Das *et al*., 2006). Several alterations in the small-intestinal morphology and function have been documented after ethanol ingestion. The permeability is probably increased, permitting entrance of possible noxious agents, which may explain some of the extra intestinal tissue damage observed in chronic alcoholism. Several enzymes located in the brush border are affected. Lactase activity depressed and perhaps results in transient milk intolerance in predisposed individuals. The activity of Gamma-Glutamyl Transpeptidase (GGT) is increased and may partly account for the GGT elevation in serum after heavy drinking. Na^+-K^+-ATPase activity is inhibited and results in a decreased absorption of substances that require active, energy-dependent transport mechanisms. The secretion of water and electrolytes may also be increased (Persson, 1991).

GASTROINTESTINAL TRACT, OESOPHAGUS AND STOMACH

After consumption the alcoholic beverages first pass through the various segments of the gastrointestinal (GI) tract. Therefore, alcohol may interfere with the structure as well as the function of gastrointestinal tract segments. It can also impair the function of the muscles separating the esophagus from the stomach, thereby favoring the occurrence of diarrhea and heartburn. Alcohol inhibits the absorption of nutrients in the small intestine and increases the transport of toxins across the intestinal walls. Alcohol-induced damage to the mucosal lining of the esophagus increases the risk of esophageal cancer (Bode and Bode, 1997).

Ethanol directly damages the mucosa of the alimentary tract in experimental animals. Gastric mucosal inflammation is observed in patients drinking alcohol chronically, while atrophic gastritis is observed only in alcohol addicted patients (Bienia *et al*., 2002). The interval between recurrent episodes of acute mucosal damage due to chronic ethanol ingestion is too short to allow complete healing of mucosal lesions. Failure to regenerate denuded epithelium would result in a decrease in the gastric secretory area. Thus, chronic alcohol abuse seems to be an etiological factor in atrophic gastritis (Segawa *et al*., 1988).

Ethanol does not cause tolerance, dependence or withdrawal in the rat, which may be due to a local rather than a systemic effect on the smooth muscle. Chronic moderate doses of ethanol impair both spontaneous and tonic contractility of the stomach and duodenal muscle without affecting ileal contraction in rats, possibly due to motility defects in the gut exposed to ethanol (Palasciano *et al*., 1995).

The symptoms of chronic inflammation and also the signs of inflammation's activity, mostly in antrum region, can be revealed by histopathological examination (Hydzik and Kosowski, 2001). The secretion of hydrochloric acid decreased both in basic conditions and after pentagastrin stimulation in alcohol addicted patients. Continuous abuse of alcohol predisposes to atrophic inflammation of the gastric mucosa and the appearance of this type of inflammatory changes is related to the duration of addiction (Bienia *et al*., 2002). Alcohol especially causes erosions. Though low doses of ethanol stimulate hydrochloric acid secretion; higher doses have no effect on its secretion. Nevertheless beer or wine stimulates acid secretion very intensively by gastrin liberation. Low concentrations of alcohol have no influence on gastric emptying, but higher concentrations delay emptying, solid meals more than liquid meals (Wolff, 1989). The secretory response of gastric acid to pure ethanol and alcoholic beverages may be different because of the non-ethanolic contents. Alcoholic beverages with low ethanol content (beer and wine) are strong stimulants of gastric acid secretion and gastrin release, the effect of beer being equal to the maximal acid output. Beverages with a higher ethanol content (whisky, gin, cognac) do not stimulate gastric acid secretion or release of gastrin. The effect of chronic alcohol abuse on gastric acid secretion is therefore not predictable (Chari *et al*., 1993).

LIVER

Ethanol is not stored in the body, as whatever is ingested is oxidized. It is metabolized entirely in the liver (Das *et al*., 2005). Alcoholic liver disease (ALD) develops as a consequence of priming and sensitizing mechanisms rendered by cross-interactions of primary mechanistic factors and secondary risk factors. Chronic alcohol abuse and its progression to ALD are associated with abnormal metabolism and low tissue or plasma levels, or both, of many micronutrients (Das and Vasudevan, 2006). Chronic alcohol consumption leads to increased sensitivity to the inhibition of respiration by nitric oxide and this results in a greater vulnerability to hypoxia and the development of alcohol-induced hepatotoxicity (Venkatraman *et al*., 2003). Alterations in the redox state during chronic ethanol consumption are associated with the oxidation of ethanol via alcohol and aldehyde dehydrogenase (Chrostek *et al*., 2005). Thus, the induction of CYP2E1 by ethanol in these cells could cause significant changes in intracellular acetaldehyde concentrations which, together with increased lipid peroxidation, may contribute to the development of alcoholic liver injury (Koivisto *et al*., 1996).

Chronic ethanol feeding damages the hepatic mitochondria by increasing mitochondrial DNA (mtDNA) oxidation, lowering mtDNA yields and impairing mitochondrial respiration. Additionally, ethanol consumption caused an increase in the levels of citrate synthase while not impacting mitochondrial protein content (Cahill *et al*., 2005).

Chronic ethanol consumption is associated with increased levels of circulating endotoxins and proinflammatory cytokines that affect liver function. A major source of the increase in circulating proinflammatory cytokines is the Kupffer cells, which are sensitized to generate Tumor Necrosis Factor alpha (TNF-alpha) through multiple mechanisms. In addition, the hepatocytes themselves are more susceptible to external stress. In isolated hepatocytes, this effect of chronic ethanol is evident in a greater sensitivity to proapoptotic challenges and, more specifically, to the cytotoxic actions of TNF-alpha. The mechanism by which hepatocytes are sensitized to external stress remains poorly characterized but may involve defects in mitochondrial function and oxidative defense mechanisms, the activation of death-promoting signaling pathways and the inactivation of survival pathways. The

stress-activated Mitogen-Activated Protein Kinase (MAPK) cascades in the onset of cell injury and their regulation by the phosphoinositide-3-kinase/Akt signaling cascade, which appears to function as the central integrating module of the stress-signaling machinery in the cell (Hoek and Pastorino, 2004).

Marked alterations in amino acid metabolism in the liver and other organs are observed in human alcoholics. This results changes in plasma and tissue levels of amino acids and may explain or contribute to hepatic encephalopathy by altering levels of intermediate products such as catecholamines and neurotransmitters (Shaw, 1978). Ethanol increases microsome cholesterol levels in the liver and the turnover of acyl moieties of phosphatidylethanolamine, sphingomyelin and phosphatidylinositol. It also induces faster phospholipid metabolism in the liver microsomes (Sanchez-Amate *et al*., 1991).

PANCREAS

Chronic ethanol ingestion appears to increase susceptibility of the pancreas to pancreatitis (Deng *et al*., 2004). It might be due to the effect on intrapancreatic digestive enzyme activation, either by sensitizing acinar cells to pathologic stimuli or stimulating the release of a secretagogue (cholecystokinin) from duodenal I cells (Lerch *et al*., 2003). An increase in pancreatic digestive and lysosomal enzyme synthesis could contribute to the development of pancreatic injury. Ethanol increases the pancreatic content of lipase but does not influence chymotrypsinogen or trypsinogen activities (Apte *et al*., 1995). Non-oxidative metabolism of ethanol resulting in the formation of fatty acid ethyl esters (FAEEs) in pancreas appears to be another of the major causes for pancreatitis (Kaphalia and Ansari, 2001).

HEART

Alcohol is a known myocardial depressant. The evidence suggests a J- or U-shaped relationship between alcohol and Coronary Heart Disease (CHD). In a dose-dependent fashion, progressive decline in left ventricular systolic function can be observed. Low to moderate doses of alcohol reduces cardiovascular risk (Agarwal and Srivastava, 2001; Lee and Regan, 2002) either by inhibiting the formation of atheroma or by decreasing the rate of blood coagulation (Agarwal and Srivastava, 2001) and this benefit may exceed the risk of hypertension or heart failure. But chronic high-dose intake of alcohol has a direct relationship to elevated blood pressure (Lee and Regan, 2002) and can lead to alcohol-induced heart muscle disease, a condition that may result in arrhythmias, cardiomegaly and congestive heart failure. (Beckemeier and Bora, 1998). Also, prolonged exposure to alcohol increases the likelihood of developing congestive heart failure (Lee and Regan, 2002). Alcohol-induced occlusion of small arteries with consequent secondary ischaemia leads to individual myocyte loss, focal fibrosis and compensatory cardiac hypertrophy (Ahmed *et al*., 1996).

BRAIN

The brain has a great cellular heterogeneity. It is one of the most membrane dense organs in the body. Acute effect of ethanol influences different kinds of movements within the membranes, which gives rise to more fluid membranes. When the lipid milieu in which the proteins are embedded is disturbed, the properties of the enzymes and receptor proteins are altered. Fluid regions are more affected than rigid ones (Alling, 1983). There is an enlargement of the cell nuclei in the endothelium of some capillaries in the brain cortex of ethanol fed rats. The number of mitochondria in the cytoplasm and of micropinocytic vesicles increases and proliferation of the smooth endoplasmic reticulum and golgi system is also noted. Considerable oedema is observed in the astrocytic processes surrounding

the vessels, with the presence of numerous mitochondria of abnormal shape and huge size. These might be due to an increased permeability of the blood-brain barrier as the result of the toxic effect of ethanol (Karwacka, 1980).

Neuroradiological studies have been demonstrated that the brains of chronic alcoholics undergo loss of both gray and white matter volumes (Brooks, 2000). In chronic alcoholism, selective vulnerability among the cells determines the final outcome of cell necrosis and myelin seems to be reduced (Alling, 1983).

Chronic alcohol abuse results in increased levels of Reactive oxygen species (ROS) and lipid peroxidation products in neurons and increased steady state levels of DNA lesions inhibit gene expression, thus causes neuronal death (Brooks, 2000). Changes in neurohormonal transmitters may account for the alterations in end organ sensitivity and secretory patterns in alcoholism. These initial pathogenetic mechanisms induce various clinical syndromes (Baratti *et al*., 1980). The pathogenesis of alcoholic neuropathy is different from central nervous system disorders and it seems that it results from a failure of the protection barrier systems in the peripheral nervous system (Parthasarathy *et al*., 2006).

SKELETAL MUSCLES

Alcohol causes reductions in protein synthesis not only in skeletal muscles, but also in skin, bone and small intestine. The reductions in protein synthesis in the skeletal muscle do not appear due to the generation of reactive oxygen species, are not prevented with nitric oxide synthase inhibitors and may be indirectly mediated by the reactive metabolite acetaldehyde. Ethanol misuse increases urinary nitrogen excretion with concomitant loss of lean tissue mass. The loss of skeletal muscle protein is one of several adverse reactions to alcohol (Preedy *et al*., 1999).

KIDNEY

The kidney is an important organ having not only excreting function but also other functions such as production of the important factors, enzymes etc. Kidney takes water-soluble exogenous substances and their metabolites from the blood and accumulates them in the cells and interstitial tissues (Sakurama, 1998). After ethanol administration, the ethanol and its metabolites go through kidneys and are excreted into urine and their content of the urine is higher than that of the blood. Upon one-week ethanol administration, swelling of glomerula and tubules, proliferation of mesangial cells and hyaline drop in tubular epithelial cells are seen in the kidney. After two-month administration of ethanol, ethanol metabolites-protein adducts and hyaline in tubular epithelial cells are observed. Atrophy of tubular epithelial cells, urinary casts and cell infiltration to interstitial tissue, thickening of basement membrane of glomerulus, Periodic Acid-schiff (PAS) positive deposits in glomerulus and proliferation of mesangial cell were observed in the kidney after six months of ethanol administration (Omoto *et al*., 1997).

TESTES

Alcohol adversely affects spermatogenesis and testicular function. Thickened capsule, atrophic seminiferous tubules and damaged germinal epithelium, multinucleated giant cells, fragmented spermatozoa and desquamated spermatocytes in the lumen of the tubules were observed in the testes. Atrophic ductules containing very few spermatozoa were observed in the epididymides of these ethanol treated animals. The serum testosterone levels are reduced in alcohol-treated animals (Klassen and Persaud, 1978), while oestradiol levels were increased in chronic alcoholic men (Gomathi *et al*., 1993).

Chronic alcohol administration resulted in an inconstant decrease in plasma testosterone levels diminished response of it to human chroinic gonadotropin (hCG) and increase in basal plasma estrogen levels in the human (Mateos *et al*., 1987).

Severe reduction of spermatogenesis was found in alcoholics, serum follicle stimulating hormone and prolactin concentrations were significantly higher among alcoholics (Lindholm *et al*., 1978). Both prolactin and gonadotropin secretion is also affected in chronic alcoholism (Mateos *et al*., 1987). Chronic alcohol administration to male animals is associated with testicular atrophy and gonadal failure. The Sertoli cell seems to be the first testicular cell injured as a result of ethanol exposure. Ethanol exposure increased Sertoli cell transferrin protein and mRNA levels and increased Sertoli cell ornithine decarboxylase mRNA and protein. These proteins are known to be important in the process of spermatogenesis (Zhu *et al*., 1997).

There is a marked reduction of the sperm forward motility and increase in the number of spermatozoa with morphological abnormalities. The lipid profiles showed a marked decrease in the total phospholipid concentration in spermatozoa, primarily in sphingomyelin, phosphatidyl choline and ethanolamine fractions. The cholesterol: phospholipid ratio in spermatozoa is increased in alcoholics. There is a decrease in total lipid, in glyceride glycerol and in free and esterified cholesterol in the seminal plasma of chronic alcoholics. These may be responsible for the fertility disorders common in chronic alcoholics (Gomathi *et al*., 1993).

Alcohol abuse may lead to testicular lipid peroxidation and its chronic use leads to both endocrine and reproductive failure. Because testicular membranes are rich in polyenoic fatty acids that are prone to undergo peroxidative decomposition, it is reasonable to consider that lipid peroxidation may contribute to the membrane injury and gonadal dysfunction in alcoholism (Rosenblum *et al*., 1989).

SKIN

Alcohol consumption and abuse can have a variety of cutaneous manifestations. In addition to the well-recognized stigmata of the chronic alcoholic patient, even early abuse can result in distinctive skin changes or exacerbate existing cutaneous disorders (Smith and Fenske, 2000). It influences thermoregulation so that body core temperature is lowered not only by automatic mechanisms (sweating and skin vasodilation) but also behaviorally (Yoda *et al*., 2005).

PREVENTIVE STRATEGIES

Therapy for alcoholism depends on the spectrum of pathological injury. Abstention is the foundation of therapy for an alcohol problem. The continuing mortality, poor acceptance of corticosteroids and identification of Tumor Necrosis Factor-alpha (TNF-α) as an integral component has led to studies of pentoxifylline and, recently, anti-TNF antibody to neutralize cytokines in the therapy of severe alcoholic hepatitis. Antioxidant therapy of alcoholics has significant promise but will require large clinical trials (Levitsky and Malliard, 2004). In view of public health interests a specific registration and licensing system for those producing or importing, distributing and selling or serving alcoholic beverages, with local or national government authorities responsible for giving licences, has proved in many societies to be a key element in controlling the level of drinking or rates of alcohol-related problems (Room *et al*., 2003).

CONCLUSIONS

Alcohol intoxication leads to a various disorders such as gastritis, gastric ulcers, fatty liver, liver cirrhosis, alcoholic hepatitis and pancreatitis. Average volume of alcohol consumption and CHD found

a J-shaped curve. Time dependent histological changes are observed in the kidney due to ethanol exposure. It adversely affects spermatogenesis and testicular functions. There is an urgent need, however, for arresting or reversing alcohol-induced organ damage at primary stages of alcoholism. This might be achieved through systematic efforts.

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