



VAGARIES OF ALCOHOLISM AND ITS CLINICAL SIGNIFICANCE

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ABSTRACT

In most countries chronic alcohol consumption is a medical problem of great magnitude with important socio- economic ramifications. Liver cirrhosis is one of the first causes of death among middle-aged subjects, especially males, and, in several populations studied, the evolution of the rate of mortality by cirrhosis is parallel to the amount of alcohol intake. Alcohol's adverse effects on the blood building, or hematopoietic, system are both direct and indirect. The direct consequences of excessive alcohol consumption include toxic effects on the bone marrow, the blood cell precursors and the mature red blood cells (RBC's), white blood cells (WBC's) and platelets. Alcohol's indirect effects include nutritional deficiencies that impair the production and function of various blood cells. The present review analyses the genetic factors altering the hepatic metabolism of alcohol, the metabolic changes produced in the liver during alcohol metabolism and their relationship with the pathogenesis of the disease, hematological changes, pharmacological interactions and various diseases associated with excessive alcohol consumption.

Keywords: Alcohol, metabolic changes, liver cirrhosis, hematological changes.

INTRODUCTION

In most countries chronic alcohol consumption is a medical problem of great magnitude with important socio- economic ramifications. Liver cirrhosis is one of the first causes of death among middle-aged subjects, especially males, and, in several populations studied, the evolution of the rate of mortality by cirrhosis is parallel to the amount of alcohol intake¹. Apart from the liver involvement, alcohol often causes neurologic, cardiac, muscular and pancreatic disease as well as a greater incidence of neoplasms in the digestive and respiratory tracts. The toxic effects of alcohol are directly related to the plasma levels achieved after alcohol intake. Three aspects should be taken into account on studying the pharmacokinetics of alcohol: its absorption in the stomach and the small intestine, its distribution throughout the organism and its elimination or metabolism. Practically all the alcohol absorbed is metabolized in the liver where it undergoes two oxidative processes during which it is first converted into acetaldehyde, its toxic metabolite, and afterwards, into acetate². As a consequence of the hepatic metabolism of alcohol a series of metabolic alterations take place which are responsible for liver damage. In addition, there are many factors which may influence alcohol metabolism and, consequently, modulate its toxic effect³.

People who abuse alcohol are at risk for numerous alcohol-related medical complications, including those affecting the blood (i.e., the blood cells as well as proteins present in the blood plasma) and the bone marrow, where the blood cells are produced. Alcohol's adverse effects on the blood building, or hematopoietic, system

are both direct and indirect. The direct consequences of excessive alcohol consumption include toxic effects on the bone marrow, the blood cell precursors and the mature red blood cells (RBC's), white blood cells (WBC's) and platelets. Alcohol's indirect effects include nutritional deficiencies that impair the production and function of various blood cells³.

The present review analyses the genetic factors altering the hepatic metabolism of alcohol, the metabolic changes produced in the liver during alcohol metabolism and their relationship with the pathogenesis of the disease, hematological changes, pharmacological interactions and various diseases associated with excessive alcohol consumption.

Genetic variations associated with alcohol metabolism

The pharmacologic and potentially pathologic effects of alcohol depend on the concentrations of ethanol and its metabolites in the body, and on the duration of exposure to these substances. Alcohol dehydrogenase (ADH) 1 (Class I ADH) is the key enzyme in alcohol metabolism *in vivo*. However, it has been demonstrated that systemic alcohol metabolism involves another pathway independent of ADH 1. This was originally called the non-ADH 1 pathway, and is thought to play a major role in alcohol metabolism for acute intoxication and for chronic drinkers. The main examples being the microsomal ethanol oxidizing system (MEOS) and catalase.

There are genetic variations for ADH2 and ADH3 encoded by different alleles. The frequency of the different ADH alleles has ethnic variations. Thus, the ADH2*1 allele predominates in black and white races, the ADH2*2 allele in oriental subjects and the distribution of ADH2*3 is



found in about of 25% of black subjects. With regard to the ADH3 polymorphism, ADH3*1 and ADH3*2 appear with about equal frequency among Caucasian subjects while the ADH3*1 allele predominates among black and oriental races.

The affinity for alcohol and the metabolic rate among the different isoenzymes differ and these genetic differences have been implicated in the pathogenesis of alcoholic liver disease. Several studies have attempted to relate the genetic polymorphism of ADH to alcohol dependence. In Asian population alcoholics were found to present a lower prevalence of the ADH2*2 and ADH3*1 isoenzymes which oxidize alcohol the most rapidly, producing a greater concentration of acetaldehyde which in turn, produces an uncomfortable sensation with facial flushing and tachycardia³.

Gastric ADH

In the human stomach the presence of class I, III and IV ADH isoenzymes of both low and high Km for ethanol has been demonstrated. The serum levels of alcohol are significantly lower when alcohol is administered orally than when the same amount is given intravenously. This difference is known as first pass metabolism (FPM) of alcohol.

Significance of first pass metabolism are,

- FPM completely disappears in patient undergoing gastrectomy, when the gastric emptying is accelerated or when alcohol is administered directly to the duodenum⁴.
- Gastric ADH is responsible for some of the ethnic and gender variations observed in alcohol metabolism which may favor its toxicity. The σ ADH is present in most Caucasian subjects while in most Asians its activity is very low or undetectable, making the FPM much lower in this population⁵.
- When alcohol is administered orally, the serum alcohol levels are significantly greater in women than in men, although these differences disappear after the age of 50 years. This lower FPM in women is related to their lower gastric ADH activity, especially of the class III isoenzyme⁶.
- Drugs such as aspirin and some H₂ receptor antagonists of histamine reduce the activity of gastric ADH and/or accelerate gastric emptying and, consequently, decrease FPM increasing the serum concentrations of alcohol and favoring its toxic effects⁷.

Non oxidative metabolism of alcohol

The non oxidative metabolism of alcohol which is capable of forming ethyl esters from the fatty acids occurs in organs such as the pancreas, liver, heart and adipose tissue which are organs in which alcohol induced lesions are often present and some of which also lack an oxidative system to metabolize alcohol.

Thus, fatty acid ethyl esters may play a role in the pathogenesis of the lesions induced by alcohol consumption³.

Metabolic changes related to ethanol oxidation by ADH

During ethanol oxidation mediated by ADH, hydrogen is transferred from the substrate to the cofactor nicotinamide adenine dinucleotide (NAD), converting it to its reduced form (NADH). The excess of reduced equivalents, mainly NADH, produces a change in the redox system of the cytosol which is demonstrated by a change in the lactate pyruvate ratio. This redox imbalance is responsible for a series of metabolic alterations which favor liver damage.

Metabolic alterations in alcoholism:

- High concentration of NADH+ H⁺ favours the conversion of pyruvate to lactate which leads to lactic acidosis and reduces the capacity of the kidney to excrete uric acid leading to hyperuricemia.
- Increase in the NADH/NAD ratio alters the glycerophosphate concentrations which favor the deposition of triglycerides in the liver. Moreover, the excess of NADH favors the synthesis of fatty acids.
- Increased acetyl CoA diverted to ketogenesis, cholesterol and fatty acid synthesis. The increased fatty acids are accumulated in the liver in the form of triglycerides and is related to different metabolic alterations such as increase in hepatic synthesis, a decrease in hepatic lipoprotein secretion, a greater mobilization of fatty acids from adipose tissue favoring their hepatic uptake and a decrease in fatty acid oxidation.

Biochemical and pathological markers of alcoholism⁸

- Aspartate aminotransferase (AST)
- Alanine aminotransferase (ALT)
- Albumin and Globulin
- Mean corpuscular volume
- Blood alcohol concentration
- Acetaldehyde adducts
- β -hexosaminidase
- The urinary ratio of the serotonin metabolites, 5-hydroxytryptophol (5HTOL) and 5-Hydroxyindoleacetic acid (5HIAA)
- γ -Glutamyl transferase
- Carbohydrate deficient transferring (CDT)

Hematological changes associated with alcoholism⁹

Alcohol causes suppression of blood cell production i.e hematopoiesis. Chronic excessive alcohol ingestion reduces the number of blood cell precursors in the bone



marrow and causes characteristic structural abnormalities in their cell. As a result, alcoholics may suffer from moderate anemia characterized by enlarged, structurally abnormal RBC's, mildly reduced numbers of WBC's and platelets.

Effect of alcohol on RBC's:

- Causes the development of vacuoles in RBC precursors
- Interferes with the activity of an enzyme ALA synthase (indirectly due to deficiency of pyridoxine) which mediates a critical step in hemoglobin synthesis causing sideroblastic anemia. Excessive alcohol intake causes macrocytosis
- Alcohol causes defects in the RBC membrane leading to the formation of stomatocytosis and spur cells which causes hemolysis
- Indirectly causes megaloblastic anemia due to dietary deficiency of folic acid

Effects of alcohol on WBC's:

- Affects the maturation of neutrophil in the bone marrow leading to neutropenia
- Interferes with the ability of the neutrophils to reach the site of infection or inflammation due to reduction in the production of leukotrienes which thereby reduces the adhesion of neutrophils to the blood vessel wall
- Impairs the function of monocyte macrophage system with clinically significant consequences

Effects of alcohol on platelets:

- Interferes with the late stage of platelet production and also shortens the life span of platelets causing thrombocytopenia
- Alcohol can interfere with the process of blood clotting at many levels; by causing thrombocytopenia, impairment of platelet function and diminished fibrinolysis
- Moderate alcohol consumption stimulates tissue plasminogen activator (TPA) activity thereby reducing the risk of inappropriate thrombus formation

Drug – alcohol interactions¹⁰

Many effects of alcohol and drug interaction are dose related, especially for products that affect the central nervous system or are metabolized by the liver. Whether or not they are drinking, chronic alcoholics have altered drug effects because of liver damage. Some of the common drugs involved in interaction with alcohol are,

- Analgesics Ex: Aspirin, Acetaminophen
- Antibiotics Ex: Erythromycin, Isoniazid
- Anticonvulsants Ex: Phenytoin

- Antihistamines Ex: Promethazine, Chlorpheniramine
- Anticoagulants Ex: Warfarin
- Antidiabetic agents Ex: Tolbutamide, Metformin
- Barbiturates Ex: Phenobarbitone
- Benzodiazepines Ex: Alprazolam, Diazepam
- Opioids Ex: Codeine, Morphine
- Tricyclic antidepressants

Disorders associated with alcohol consumption^{10, 11}

- Alcohol consumption in diabetics can result either in hyperglycemia or hypoglycemia, depending on the patient's nutritional status.
- In hyperlipidemic patients, alcohol consumption may exacerbate hyperlipidemia, because alcohol inhibits fat metabolism. As a result, the production of certain molecules called very low density lipoprotein (VLDL) particles is increased.
- In hypertension, alcohol is known to cause a dose-dependent elevation in blood pressure.
- In the brain alcohol initially acts as stimulant by sedating inhibitory nerves, later has depressive action.
- Alcohol increases urine output mainly acting on pituitary gland depressing the production of antidiuretic hormone vasopressin. The loss of water along with minerals such as potassium, magnesium, calcium and zinc leads to nerve and muscle incoordination.
- Alcohol consumption during pregnancy has effects on foetus causing a severe disorder called as Fetal Alcohol Syndrome (FAS).
- Excessive alcohol consumption can lead to various effects on liver such as fatty liver, alcoholic hepatitis and cirrhosis
- Alcoholism can lead to development of cancers in mouth, throat, esophagus and lungs.
- Impaired immune function, malnutrition and osteoporosis.

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