

## **The Effect of Alcohol Consumption on Liver Enzymes, High Density Lipoprotein Cholesterol and Genetic Aspects**

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### **ABSTRACT**

**Background:** Health problems related to life-style and behavior are increasingly common in modern societies. Chronic alcoholism and its related disorder are one of the major problems in the world. Chronic alcohol abuse will cause the drinker to lose control of his or her drinking. The social problems arising from alcoholism are serious and caused by the pathological changes in the brain as well as psychiatric disorder are common in alcoholic with as many as 25 percent suffering from severe psychiatric disturbances. Prolonged alcohol consumptions affect the liver enzymes such as Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT), Alkaline phosphatase (ALP) and Gamma Gutamyltransferase (GGT). In this study we found that genetic polymorphism of the patatin like phospholipase-3 I148M variant (rs738409 C>G) encoding for an isoleucine to methionine substitution, a gene coding for a transmembrane protein most prominently expressed in the hepatocytes due to excessive alcohol consumption. The effect of alcohol consumption on lipoprotein in cholesterol transport as well as novel effects of lipoproteins on vascular cell wall, comprise a complex mechanism through which alcohol is cardioprotective.

**Aim:** To recognize which factors affect of alcohol consumption on liver enzymes, High density lipoprotein cholesterol and genetic aspects, in this light of current knowledge on this matter.

**Methods:** We performed a structured literature review identifying studies focusing on the effect of alcohol consumption on the liver enzymes, HDL-Cholesterol and other factors.

**Results:** In addition to the prolonged alcohol intake and alcohol consumption patterns, such as gender, genetic background, oxidative stress, metabolism abnormalities play a key role in the effect of liver enzymes, HDL- cholesterol and genetic aspects as well as health related disorder.

**Conclusions:** Understanding the risk factors of excessive alcohol consumption on liver and liver enzymes and high density lipoprotein cholesterol. Moderate alcohol intake is beneficial for heart related problems. Excessive alcohol consumption can adversely affect every organ in the body. There is evidence that chronic consumption increase the risk of upper respiratory and upper digestive tract malignancies and breast cancer.

**Key Words:** Alcohol consumption, Liver enzymes, High density lipoprotein cholesterol, HDL-Cholesterol, Genetic aspect.

### **INTRODUCTION**

In chemical terminology alcohol is a large group of organic compounds, which are derived from hydrocarbons and contain one or more hydroxyl (-OH) groups. Ethanol (C<sub>2</sub>H<sub>5</sub>OH ethyl alcohol) is one of this class of compounds, and is the main psychoactive ingredient in alcoholic

beverages. <sup>[1]</sup> Alcohol or ethanol is an intoxicating ingredient found in beer, wine and liquor. Alcohol is produced by fermentation of yeast, sugar and starches. It is formed when yeast ferments sugar in different foods for example: - wine is made from grapes, beer from malted barley, cedar from apples, and vodka from potatoes. <sup>[2]</sup>

Alcoholism is the dependence on excessive amounts of alcohol, associated with a cumulative pattern of deviant behaviors. Alcoholism is a chronic illness with a slow, insidious onset, which may occur at any age. The cause is unknown, but genetic, cultural and psychosocial factors are suspect and families of alcoholics have a higher incidence of the disease. [3] Chronic alcoholism and its related disorders are one of the major problems in the world. Chronic alcohol abuse will cause the drinker to lose control of his or her drinking. There may be plan to have only a few drinks, but in the end, the drinker loses control over this very valid plan and drinks much more than intended. Chronic alcohol abuse can lead to feelings of guilt and shame as well as to broken relationships and broken families due to family's lack of control over the alcohol intake. [4] Prolonged alcohol consumption affects the liver enzymes. Four enzymes are measured in the laboratory to evaluate function of the liver. These enzymes include Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT), Alkaline Phosphatase (ALP), and Gamma Glutamyl-Transferase (GGT). The first two are known together as transaminases and second two are known together as cholestatic liver enzymes. Elevation in any of these enzymes can indicate the presence of liver disease. Elevation of the transaminases can occur with alcoholic liver disease and fatty liver, conditions that can result from excessive alcohol intake. Elevation of the cholestatic liver enzymes can also occur with alcoholic liver disease. [5] AST catalyze transamination reaction. AST exists in two different isoenzyme forms, which are genetically distinct, the mitochondrial and cytoplasmic form. AST is found in highest concentration in heart compared with other tissues of the body such as liver, skeletal muscle and kidney. [6] Normal level of serum AST is 0-40U/L. Elevated mitochondrial AST is seen in extensive tissue necrosis during myocardial infarction and also seen in chronic liver disease. About 80% of AST activity of the liver disease is contributed by

mitochondrial isoenzyme. [7] However the ratio of mitochondrial AST to total AST activity has diagnostic importance in identifying the liver cell necrotic type condition and alcoholic hepatitis. [8] ALT is found in kidney, heart, muscle and highest concentration in liver compared with other tissues of the body. ALT is purely cytoplasmic catalyzing the transaminase reaction. Normal level of serum ALT is 0-40U/L. Any type of cell injury can increase ALT levels. Marked elevations of ALT levels greater than 500 U/L are observed most often in persons with diseases that affect primarily hepatocytes such as hepatitis, ischemic liver injury and non toxic-induced liver damage. [9] Viral hepatitis like A, B, C, D, and E may be responsible for a marked increase in aminotransferase levels. The increase in ALT associated with hepatitis C infection tends to be more than associated with hepatitis A or B. [10] In a recent study it was found that the hepatic fat accumulation in childhood obesity and nonalcoholic fatty liver disease causes serum ALT elevation. Moreover increased ALT level was associated with reduced insulin sensitivity, adiponectin and glucose tolerance as well as increased free fatty acids and triglycerides. [11] Gamma-glutamyl-transferase, catalyzes the transfer of the gamma-glutamyl group from peptides and compounds that contain it to the same accepters. [12] The gamma-glutamyl acceptor is the substrate itself, some amino acid or peptides or even water in which case simple hydrolysis takes place. Even though renal tissue have the highest concentration of GGT, the enzyme present in serum appears to originate primarily from the hepatobiliary system. GGT is a sensitive indicator of the presence of hepatobiliary disease, being elevated in most subjects regardless of cause. [13] ALP (orthophosphoric monoester phosphohydrolase) catalyzes the alkaline hydrolysis of a large variety of naturally occurring and synthetic substrates. ALP activity is present in most organs of the body and is especially associated with membrane and cell surfaces

of small intestine, proximal convoluted tubules of the kidney, in the bone, liver and placenta. Elevations in serum ALP activity commonly originate from one or more of the sources: the liver and bone. The response of the liver to any form of biliary tree obstruction induces the synthesis of ALP by hepatocytes. Some of the newly formed enzymes enter the circulation to increase the enzyme activity in serum. [14] The elevation tends to be more notable in extra hepatic obstruction than in hepatic obstruction. Liver diseases that principally affect parenchymal cells such as infectious hepatitis, typically show only moderate increase or even normal serum ALP activity. [15] High-density lipoproteins cholesterol (HDL-C) is one of the five major groups of lipoproteins. Lipoproteins are complex particles composed of lipids and proteins in varying proportions, which transport lipids from one tissue to the other through plasma. [16] HDL-C serves as carrier of cholesterol from peripheral tissues to liver for its degradation and excretion (Scavenger action). HDL contains apoproteins AI and AII. There is continuous exchange of apoproteins apo CII and apo E between HDL-C and other lipoproteins like chylomicrons and VLDL. [17]

### **Epidemiology of alcohol use disorder**

According to Organization for Economic Cooperation and Development (OECD) report released in May 2015, alcoholism increased by about 55 percent between 1992 and 2012. It is a continuously rising and is a cause of concern among the youth of the World. [18] In 2014, the World Health Organization released its Global Status report on Alcohol and Health. According to the report, about 38.3 percent of the world's populations consume alcohol regularly. On an average an individual consumption amounts to 6.2 liters of alcohol every year. According to the WHO report published in 2010, 30 percent of India's population, (just less than a third of the country's population) consumed alcohol regularly. Some 11 percent are moderate to

heavy drinkers. The average Indian consumes about 4.3 liters of alcohol per annum. The rural average is much higher at about 11.4 liters a year. [19] Excessive alcohol consumption is ranked as one of the top five risk factors for death and disability worldwide. [20] 2.5 million deaths and 69.4 million annual disability adjusted life years were attributed to harmful alcohol abuse. [21] Almost 9% of adults in the United State meet the criteria for an alcohol-use disorder. [22] Annually about \$223.5 billion is spent in treatment of alcohol use disorders. [23] There is a strong correlation between the prevalence of alcoholic liver disease (ALD), specifically cirrhosis, and a country's annual per capita alcohol consumption. Eastern European countries have the highest annual per capita consumption (15.7 L per person), while North Africa and the Middle East have the lowest annual per capita consumption (1.0 L per person). [24] In the United States, the estimated annual per capita consumption of alcohol is 8.4 L per person. [25] Countries with higher per capita consumption have the highest rates of ALD. ALD caused nearly five lakh deaths worldwide in 2010, and 14.5 million disability adjusted life years with alcoholic cirrhosis comprising 47.9% of all liver cirrhosis death. [24] In the United State alone, nearly thirty five thousand adults died from liver cirrhosis in 2009 out of which 48.2% of deaths were due to alcohol. [26]

### **Alcohol consumption and health problems**

Excessive alcohol drinking is a global problem which compromises both individual and social well-being. Almost all tissues in the body are affected, and consequently it has been shown to be closely related to more than 60 distinct medical conditions, including a wide array of both physiological and mental problems. [27, 28] The impact of ethanol intake on diseases and various types of tissue injury is dependent on two separate but related dimensions of drinking, namely the amount of alcohol consumed and the pattern of drinking. A chronic heavy drinking pattern

generates different types of health effects from those created by acute (binge) drinking, while moderate drinking has even been thought to have some beneficial effects on cardiovascular health. [29-31] Ethanol is a simple water-soluble molecule. Upon ingestion, it is absorbed rapidly throughout the gastrointestinal tract, mainly in the small intestine. [32] It is freely distributed in the body, especially to organs with a rich blood supply such as the brain and lungs. Exposure to alcohol is greatest in the liver, since blood is received directly from the stomach and small bowel via the hepatic portal vein. [33] As ethanol is mostly metabolized in the liver, this organ is a major target for ethanol toxicity. [27] Alcoholic liver disease is currently a highly prevalent group of hepatic diseases in Finland, causing about 1,000 deaths per year. [34] In addition, there is numerous health problems related to chronic alcohol effects on extra hepatic tissues. A significant proportion of the alcohol-related disease burden is also due to acute alcohol intake, including unintentional and intentional injuries, road traffic accidents, violence and suicides.

### **Other effects of alcohol consumption on health**

#### *Short term effects*

The short term effects of alcohol consumption (beer, wine, or other alcoholic beverages), range from a decrease in anxiety and motor skills at lower doses to intoxication (drunkenness), unconsciousness, anterograde amnesia (memory blackouts) and central nervous system depression at higher doses. Cell membrane is highly permeable to alcohol which diffuse into nearly every cell from the blood. [35]

#### *Long term effects*

The long term use of alcohol is capable of damaging nearly every organ and system in the body. [36] Chronic alcohol abuse has serious effects on physical and mental health. It can lead to wide range of neuropsychiatric or neurological

impairment, cardiovascular disease, and malignant neoplasms. [37]

#### *Psychiatric effects*

Psychiatric disorders are common in alcoholics with as many as 25 percent suffering from severe psychiatric disturbances. The most prevalent psychiatric symptoms are anxiety and depressive disorders. [38] Psychiatric disorders differ depending on gender. Women who have alcohol abuse disorder often have a co-occurring psychiatric diagnosis such as major depression, anxiety, panic disorder, bulimia, and border line personality disorder, whereas men have a co-occurring diagnosis of antisocial personality disorder, bipolar disorder, schizophrenia, impulse disorder. [39]

#### *Social effects*

The social problems arising from alcoholism are serious and caused by the pathological changes in the brain and intoxication effects of alcohol. [40] Alcohol abuse is associated with increased risk of committing criminal offences, including child abuse, domestic violence, rape, burglary, and assault. [41]

### **Genetic aspects of alcohol-related health problems**

Unlike many other chronic liver diseases, alcoholic liver disease is potentially avoidable, since excess alcohol consumption is a prerequisite for its development. However, alcohol consumption per se may not be the only explanation, since alcoholic liver disease progression is sometimes seen only in a minority of heavy drinkers. Although liver steatosis evolves in most heavy drinkers, only about 30% develop significant necroinflammation and fibrosis, out of which 10% progress to cirrhosis. [42] This variability in the natural course is believed to result from a complex interplay between environmental, individually acquired and inherent modifying factors.

A recent genome-wide association study identified a genetic polymorphism of the patatin like phospholipase-3 I148M variant (rs738409 C>G) encoding for an

isoleucine to methionine substitution, a gene coding for a transmembrane protein most prominently expressed in the hepatocytes. [43] This variant leads to *in vivo* triglyceride accumulation in hepatocytes, thus appearing to be the strongest determinant of human steatosis. [44] This variation was also found to be associated with elevated levels of liver enzymes in healthy subjects and with disease severity, especially steatosis and fibrosis, in non-alcoholic fatty liver disease. [45, 46] It also confers a higher risk of cirrhosis and liver damage in alcoholic liver disease. [47, 48] Several other genetic variants have been suggested to contribute to individual susceptibility to ALD. These include variants of alcohol-metabolizing enzymes, genes involved in regulating oxidative stress and those involved in endotoxin-mediated inflammation. Polymorphisms in the alcohol dehydrogenase and acetaldehyde dehydrogenase (ALDH) genes may affect the rates of acetaldehyde generation and metabolism and thereby influencing acetaldehyde toxicity. Some enzyme variants may metabolize ethanol at a faster rate, or may be unable to process acetaldehyde. Accumulation of acetaldehyde, even after small amounts of ethanol, causes a condition known as Oriental flushing syndrome, with clinical manifestations that include flushing, sweating, tachycardia, nausea and vomiting. [49] Gene variants underlying this syndrome are commonly found in Asians but rarely in Caucasians. [50] In addition, a low ALDH activity phenotype increases the risk of upper digestive, head and neck cancers, and the risk of malignancies in mainly Japanese population. [51, 52] In addition, there may be racial differences in the sensitivity of the liver to different toxic stimuli, e.g. alcohol-induced acetaldehyde accumulation, or to the risk of alcohol consumers gaining weight. [53] Variations in genes that encode antioxidant enzymes, cytokines and other inflammatory mediators may also have a role in disease susceptibility. [54, 55]

## **Effect of alcohol consumption on liver enzymes**

### *Gamma-gutamyltransferase (GGT)*

Gamma-gutamyltransferase (GGT) is a membrane-bound glycoprotein enzyme derived mainly from the hepatocytes and biliary epithelial cells, renal tubules, pancreas and intestine. [56] Increased serum GGT activity has long been used in clinical practice as a marker of both liver dysfunction and excessive alcohol intake. [57] GGT is known to increase in all forms of liver disease, especially in cases of biliary obstruction, with small increases (2–5 times normal) observed in connection with fatty liver, so that GGT is of limited value for the purpose of screening alcohol consumption per se in patients with non-alcoholic liver diseases or in hospitalized patients, for instance. [58,59]

### *Serum aminotransferase (ALT, AST)*

Hepatocellular injury, whether acute or chronic, results in an increase in serum concentrations of aminotransferases. Alanine aminotransferase (ALT) originates primarily from the hepatocytes, whereas Aspartate aminotransferase (AST) is found additionally in the heart, skeletal muscle tissue, kidney and brain. As a consequence, serum AST may also increase in response to pathological processes in the heart or skeletal muscle, while serum ALT is considered a fairly specific marker of liver disease. [60] It has also been suggested that alterations in the relative activities of AST and ALT may be related to the occurrence of hepatic mitochondrial damage and skeletal or cardiac muscle injury (alcoholic myopathy), which are common among alcoholic patients. [61] However, an AST/ALT ratio greater than two characteristically is present in alcoholic hepatitis.

### *Alkaline phosphatase (ALP)*

Alkaline phosphatase (ALP) is an enzyme that transports metabolites across cell membranes. Pathological elevations are commonly observed in liver and bone diseases, although the enzyme may originate from several other tissues. [62] The synthesis

and release of hepatic ALP is stimulated by cholestasis, and when released, its half-life in the circulation is about 7 days.<sup>[63]</sup> Since elevated ALP is a somewhat unspecific parameter, it needs to be interpreted in the context of a clinical diagnosis and other laboratory markers.

### **Relation between alcohol consumption and high density lipoprotein cholesterol**

Increased high-density lipoprotein cholesterol (HDL-C) levels promote a reverse transport of lipids that stabilizes atherosclerotic plaque. Approximately half of cardiovascular benefits from moderate alcohol consumption are from increased levels of high-density lipoprotein cholesterol (HDL-C), decreased levels of low-density lipoprotein cholesterol (LDL-C), and a lowering of plasma apolipoprotein concentration.<sup>[64]</sup> Red wine drinking, at 47 g/d, is associated with a 27% increase in HDL cholesterol. Regular wine consumption is associated with 30 to 90% higher levels of polyunsaturated lipids in HDL and with a 27% increase in the cholesterol esterification rate.<sup>[65]</sup> During three weeks of moderate alcohol consumption, an increase in apo A-I is followed by an increase in HDL cholesterol. The kinetics and sequence of these increases may be an additional mechanism of action underlying the reduced coronary heart disease risk in moderate drinkers.<sup>[66]</sup> Moderate alcohol intake decreases clot formation by multiple additive mechanisms. Moderate alcohol consumption reduces platelet aggregation, decreases fibrinogen levels, plasma viscosity, von Willebrand factor, and factor VII.<sup>[67-69]</sup> Regular moderate alcohol consumption has no significant effect on fibrinolysis, as opposed to higher levels of consumption.<sup>[70]</sup> Heavy alcohol consumption can adversely affect essentially every organ system. There is evidence that chronic consumption of as little as two drinks per day increases the risk of upper respiratory and upper digestive tract malignancies and breast cancer. The relative risk of oral and pharyngeal cancers associated with two drinks per day is 1.75;

the same level of alcohol consumption is associated with a relative risk of 1.51 for esophageal cancer. The relative risk of colon cancer associated with two drinks per day is 1.08. In a meta-analysis of 53 studies the relative risk of breast cancer in women was 1.32 for an average intake of 35 to 44 g/d of alcohol per day, and 1.46 for those consuming more than 44 g/d. The concurrent use of alcohol and tobacco conferred no additional risk of breast cancer.<sup>[71-72]</sup>

### **CONCLUSIONS**

Unhealthy alcohol consumption remains a main problem for the public health and is responsible for a high rate of morbidity, affecting various organ and systems, and mortality. The pathophysiology of ALD is quite complex, encompassing factors related to genetics, gender, ethnicity, consumption patterns and co-morbid conditions. From such a composite interplay, several clinical manifestations ensue, ranging from a benign condition, such as steatosis, to deadly diseases, such as cirrhosis and hepatocellular carcinoma. Prolonged alcohol consumption affects the liver enzymes. Increased serum GGT activity has long been used in clinical practice as a marker of both liver dysfunction and excessive alcohol intake. Elevated serum aminotransferase levels can be found in asymptomatic patients for a variety of reasons, e.g. excessive alcohol intake, overweight, viral or autoimmune hepatitis, hemochromatosis, Wilson's disease, alpha 1-antitrypsin deficiency, celiac disease, genetic disorders in muscle metabolism, acquired muscle diseases, or strenuous exercise. Alkaline phosphatase is an enzyme that transports metabolites across cell membrane. If a person taking excessive alcohol consumption it can raise in the blood because ALP is present in liver. In addition, alcohol consumption may alter the activities of plasma proteins and enzymes involved in lipoprotein metabolism. Alcohol intake also results in modifications of lipoprotein particles; specifically, low sialic

acid content in apolipoprotein components of lipoprotein particles and acetaldehyde modification of apolipoprotein. The effects of alcohol on lipoproteins in cholesterol transport, as well as the novel effects of lipoproteins on vascular cell wall, comprise a complex mechanism through which alcohol is cardioprotective. Moderate alcohol intake is beneficial for health. Moderate alcohol consumption reduces platelets aggregation, decrease fibrinogen levels, plasma viscosity, von Willebrand factor, and factors VII. Heavy alcohol consumption can adversely affect every organ in the body. There is evidence that chronic consumption increase the risk of upper respiratory and upper digestive tract malignancies and breast cancer.

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