Title page

Alcohol use, Vascular Disease and Lipid-Lowering Drugs

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Running title page

Alcohol and Lipid-Lowering Drugs

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Abstract

Many epidemiological and clinical studies have shown that light-to-moderate alcohol (Alc) consumption is associated with reduced risk of coronary heart disease (CHD) and total mortality in middle-aged and elderly men and women. The plausible mechanisms for the putative cardioprotective effects include increased levels of high density lipoprotein cholesterol, prevention of clot formation, reduced platelet aggregation, promotion of blood clot dissolution and lowering of plasma lipoprotein (a) concentration. Individuals needed to be treated with lipid-lowering drugs, such as dyslipidemic or CHD patients may benefit from these effects of Alc. Since hypolipidemic treatment is usually continued for life, an important issue is the suitability of Alc consumption in these patients. In the present review, the beneficial effects of Alc consumption on CHD risk, its side effects, as well as its safety and suitability when co-administered with hypolipidemic drugs, are discussed.
Introduction

Many epidemiological and clinical studies have shown that light-to-moderate alcohol (Alc) consumption is associated with reduced risk of coronary heart disease (CHD) and total mortality in middle-aged and elderly of both genders (Rimm et al., 1999; Rehm et al., 2003). Men and women who consume a moderate amount of Alc, defined as 1-4 and 1-2 drinks respectively, for 5 or 6 days per week had substantial reduction of major coronary events compared to non-drinkers [odds ratios: men 0.31 (95% confidence interval 0.22 to 0.45), women 0.33 (0.18 to 0.59)] (McElduff and Dobson, 1997). One thousand years ago, a “prescientific” observation of Alc’s beneficial effect was described by Hildegard of Bingen (Germany, 1098-1179), who applied a special “wine recipe” in order to treat cardiovascular disease (Böhm et al., 2004). The inverse alcohol-atherosclerosis association was also pointed out by pathologists early in the previous century. At the same time, there is no doubt that treatment with lipid-lowering drugs has decreased cardiovascular disease mortality (Collins et al., 2003; Harrington, 2004). Treatment with lipid-lowering drugs is recommended for lifetime, unless there are contraindications. The question is whether physicians can also recommend social Alc consumption to their patients while they are on lipid-lowering drug therapy. This review focuses on the issue of concomitant Alc consumption and lipid-lowering drug use.

Alc and CHD

The risk of death from all causes has been found to be significantly lower among men who drink moderately on a regular basis when compared with abstainers (Rimm et al., 1999; Rehm et al., 2003). When data from various studies are combined, there appears to be a decline in the risk of myocardial infarction at doses of up to 1 drink per day, with little further change in this risk with increased Alc intake (Rimm et al., 1999). Makela et al. (1997) observed that light-to-moderate Alc consumption was associated with a 12-14% reduction in CHD deaths among Finish men aged 30–
69 years. In the metanalysis of Rimm et al. (1999), a 30 g daily intake of Alc was associated with a 25% reduction in the risk of CHD. This benefit was attributed to lipid, lipoprotein and fibrinogen alterations. The dose-response curve of Alc consumption in relation to total mortality and CHD risk is usually found to be J- or U-shaped (Andreasson, 1998; Gaziano et al., 2000). The risk is higher in individuals not consuming any Alc than in cases of moderate consumption, with the lower risk observed at 20 g per day. This risk is increased in individuals that consume higher doses of Alc. When the average consumption per day rises to over 70 g, the risk becomes greater than that for abstainers (Rehm et al., 2003). The relationship with CHD mortality was found to be inverse or L-shaped with apparent risk reductions even in the highest category of ≥2 drinks per day (Gaziano et al., 2000). Moreover, the pattern of drinking seems to differentiate Alc’s effect on CHD. While regular light-to-moderate drinking is beneficial for CHD risk, an irregular pattern of heavy drinking (≥5 drinks for women and ≥9 for men on one occasion) seems to be related to major coronary events (McElduff and Dobson, 1997), as well as other types of cardiovascular death such as stroke and sudden cardiac death (Rehm et al., 2003). Finally, people who accompany Alc drinking with meals or snacks had a lower risk for CHD (Rehm et al., 2003).

**Biological mechanisms responsible for the beneficial effect of Alc**

It has been proposed that Alc’s protective effect is mediated through the increase of high density lipoprotein (HDL) cholesterol since its levels are inversely related to CHD (Agarwal, 2002). According to Rimm et al. (1999), consuming 30 g Alc per day increases HDL cholesterol levels by 4 mg/dl (0.10 mmol/L) which in turn is equivalent to an estimated 17% reduction in CHD risk. This Alc-induced increase in HDL cholesterol levels is attributed to the following mechanisms. Firstly, Alc induces the hepatic synthesis of apolipoprotein (apo) AI and apo AII (the main components of HDL particles) (Agarwal, 2002; Rimm et al., 1999). It has been estimated that an average individual consuming 30 g of Alc per day would show an 8 mg/dl (0.20 mmol/L) increase in the plasma concentration of apo AI (Rimm et al., 1999). Apo AI constitutes the
precursor of HDL particle formation. Through its binding to ATP-binding cassette transporter A1, phospholipids attach to apo AI to form disk-like particles (pre-β-HDL) (Kolovou et al., 2006). Free cholesterol from peripheral cells then effluxes to pre-β-HDL which are transformed to mature-spherical HDL after cholesterol esterification (Kolovou et al., 2006). Secondly, Alc metabolism raises triglyceride (TG) concentration, which in turn induces the secretion of TG-rich lipoproteins by the liver, and increases the activity of TG lipase. Concomitantly, the lipolysis of TGs in lipoprotein particles [such as very-low-density lipoproteins (VLDL) and chylomicrons] increases the flow of cholesterol from these particles to HDL particles (Rimm et al., 1999). Thirdly, Alc reduces cholesterol ester transfer protein (CETP) activity leading to reduced transfer of cholesteryl ester from the core of HDL to more atherogenic particles, in exchange for TGs. Given that TG-rich HDL particles are prone to catabolism, Alc indirectly decreases the removal of circulating HDL cholesterol by the latter mechanism (Fumeron et al., 1995). Summarising, Alc by promoting the production of HDL constituents, by enhancing the flow of cholesterol to HDL particles and by delaying their catabolism, favours raising HDL cholesterol concentration (Figure 1). Early observations suggested that Alc mainly raised levels of HDL-3 particles, not HDL-2, but more recent studies have found that both subfractions are increased (Rimm et al., 1999).

Increased HDL cholesterol levels can partially explain the protective effect of alcoholic beverages. Other biological mechanisms underlying Alc’s protective effect include the increase of paraoxonase activity, the reduction of lipoprotein (a) levels, the inhibition of blood clotting and platelet aggregation, the improvement of insulin sensitivity, the lowering of plasma homocysteine levels, the oestrogen levels increase and the reduction of stress. Moreover, moderate alcohol intake has been reported to confer protection against inflammation, a process with a fundamental role in the initiation, progression and the thrombotic complications of atherosclerosis. Such functions are extensively considered in other reviews (Agarwal, 2002; Imhof & Koenig, 2003).
Side effects of Alc

The proposed cardiovascular benefits of Alc consumption must be evaluated against numerous adverse effects. Beyond 2 drinks per day, no further reduction in cardiovascular mortality is observed (Gaziano et al., 2000). This appears to be due to increases in Alc-related medical disorders such as: 1) Cardiovascular system; hypertension, cardiomyopathy, atrial and ventricular arrhythmias, hyperlipidemia, 2) Central nervous system; acute delirium, hepatic encephalopathy, cerebrovascular accidents, cerebral atrophy, 3) Muscle-skeletal system; myopathy, hyperuricemia, 4) Gastrointestinal system; fatty liver, hepatitis, cirrhosis, hepatoma, ascites, 5) Hematopoietic system; anemia, coagulation abnormalities, leucopenia, thrombocytopenia. Binge drinking is associated with impaired left ventricular function and arrhythmias (the most frequent paroxysmal atrial fibrillation - the “holiday heart syndrome”) (Greenspon and Schaal, 1983). An increased incidence in myocardial infarction on Mondays has been noted. Several explanations for this observation have been proposed, such as an increase in stress due to the transition from leisurely pace of life on weekends to a work schedule (Spielberg et al., 1996). Although this explanation may account for the higher occurrence of cardiovascular deaths on Mondays, another important factor is heavy or binge drinking during the weekend (Evans et al., 2000). Irregular heavy drinking is also related to stroke and sudden cardiac death (Rehm et al., 2003). These adverse effects of Alc can be attributed to increased clotting, rise in low density lipoprotein (LDL) cholesterol concentration and lower threshold for ventricular fibrillation that occur with heavy drinking (Rehm et al., 2003).

Alc is one of the factors most frequently associated with increased liver enzyme activity in both animals (Kolovou et al., 2003; Kolovou et al., 2004; Kolovou et al., 2005) and humans (Kraemer et al., 2003). In our studies (Kolovou et al., 2003; Kolovou et al., 2004; Kolovou et al., 2005) with rats, Alc administration caused an increase in aspartate aminotransferase (AST) levels,
similar to Kamimura et al. (1992) who observed two and three fold increases in plasma alanine aminotransferase (ALT) and AST levels in Alc-fed male Wistar rats.

The association between Alc intake and Alc-induced liver disease in humans is well known. The Italian Dionysos study showed that Alc is suspected to cause the 23% of all cases of liver disease, with a dose-dependent increase in the risk of developing liver disease (Bellentani et al., 1997). Other investigators (Kraemer et al., 2003) also showed elevation of aminotransferase levels in humans. Conversely, investigators from Japan did not show a strong relationship between Alc consumption and serum liver enzyme activity; specifically AST and ALT (Nakamura et al., 1998).

The close relationship between ethanol consumption and liver function is due to the fact that more than 80% of ingested Alc is metabolized in the liver (Uzun et al., 2005). Alcohol is catabolized through two different pathways according to the mode of consumption (Figure 2). After moderate consumption, ethanol is oxidized to acetaldehyde in the cytosol via the action of alcohol dehydrogenase, by a concomitant conversion of nicotinamide adenine dinucleotide (NAD) to reduced NADH. Acetaldehyde is further oxidized by aldehyde dehydrogenase to acetate (Lieber, 2003). During both the above oxidising processes, nitric oxide radicals are also formed (Uzun et al., 2005). In the case of chronic heavy consumption, the microsomal ethanol-oxidizing system is activated. The enzyme P450 cytochrome of this system converts ethanol to acetaldehyde. This reaction relies on the availability of oxygen and reduced nicotinamide adenine dinucleotide phosphate (NADPH) and results in the production of reactive oxygen species (Lieber, 2003). This first step of oxidation is catalyzed mainly by CYP450 2E1, while CYP450 1A2 and CYP450 3A4 variants have a minor contribution (Lieber, 2003). Acetaldehyde may be subsequently oxidized to acetate by the CYP450 2E1 variant. However, the bulk of acetaldehyde is metabolized in the mitochondria via aldehyde dehydrogenase (Terelius et al., 1991).
Acetaldehyde is a highly reactive molecule that may alter the intracellular redox status generating oxidative stress (Dupont et al., 2000). Nitric oxide radicals and reactive oxygen species, also produced by ethanol breakdown, contribute to this latter condition (Uzun et al., 2005; Lieber, 2003). Oxidative stress leads to protein deactivation, inactivation of essential enzymes, damage of antioxidants, such as glutathione and vitamin E, triggering of inflammatory response and alteration of fat breakdown (Lieber, 2003; McCuskey et al., 1995). Acetate released into the plasma is shown to decrease lipolysis in peripheral tissues by 53% and the whole-body lipid oxidation by 73% (Siler et al., 1999). Excess NADH concentration reduces fat breakdown and generates fatty acids giving rise to fat accumulation in liver, a fact that raises TG serum levels by increased production and secretion of VLDLs (Ginsberg et al., 1974). The chronic excessive consumption of Alc has been associated with hepatosteatosis, liver fibrosis and cirrhosis. Liver cirrhosis is related with the overall volume of Alc intake (Kozarevic et al., 1983).

Furthermore, epidemiological data clearly show that increasing Alc drinking is associated with higher mean blood pressure and/or hypertension (Grobbee et al., 1999). On the other hand, the short-term lowering of blood pressure caused by Alc is also known. Alc’s effect on blood pressure varies according to chronicity and amount of intake. A J-shaped association has been proposed for the relationship between Alc and blood pressure (Gillman et al., 1995). Many studies support that there is a threshold of 2 to 3 drinks daily below which Alc may exert a beneficial effect (Beilin et al., 1996). However, a linear correlation has also been reported. Specifically, for each 100 g per week increase in Alc consumption, diastolic pressure increased by 0.92 mmHg in men and by 1.5 mmHg in women with a plateau phase at 500 g per week (Cooke et al., 1982).

Long-term heavy Alc intake in both sexes and all races is the leading cause of a nonischemic, dilated cardiomyopathy, referred to as alcoholic cardiomyopathy. Individuals consuming >90 g of Alc per day for >5 years are at risk of developing asymptomatic alcoholic cardiomyopathy (Piano, 2002).
Interestingly, many studies also reported an association between Alc consumption and different types of cancer. Recent meta-analyses suggest that an average of 25 g of Alc per day is related to increased risk for cancer at the following sites: oral cavity, pharynx, esophagus, stomach, colon rectum, liver and larynx (Rehm et al., 2003). Alc consumption may increase blood oestradiol levels in postmenopausal women who are on oestrogen replacement therapy, increasing the risk of breast cancer (Ginsburg, 1999). However, the risk of breast cancer is independently related with Alc consumption in women and in particular with irregular heavy drinking (Rehm et al., 2003).

**Alc Consumption and Lipid-Lowering Drugs**

Large clinical trials proved that lipid-lowering drugs can decrease CHD deaths (Collins et al., 2003; Harrington, 2004; Baigent et al., 2005). Individuals needed to be treated with lipid-lowering drugs, such as dyslipidemic or CHD patients can benefit from the effect of Alc on cardiovascular risk (Rimm et al., 1999; Makela et al., 1997; McElduff and Dobson, 1997). Since Alc consumption could be advised in such patients and hypolipidemic treatment is usually continued for life, an important issue is the safety of such a combination. Firstly, the safety of this combination is questioned, since it is well known that liver function can be disturbed by both Alc and hypolipidemic drugs. Nevertheless, there are animal studies, where this combination proved to be safe on a chronic basis as discussed below (Kolovou et al., 2003; Kolovou et al., 2004; Kolovou et al., 2005). Secondly, drug effectiveness could be influenced, because chronic Alc use causes secondary hypertriglyceridemia (Ginsberg et al., 1974). Moreover, Alc’s metabolism may affect the breakdown and elimination of certain medications, including hypolipidemic drugs, through microsomal ethanol-oxidising system and consequently contribute to harmful interactions (Dupont et al., 2000; Lieber, 2003).

**Statins**
Statins, inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, are well established lipid-lowering agents. Statins decrease serum total cholesterol levels by inhibiting hepatic cholesterol biosynthesis. Thus, statins upregulate hepatic LDL receptors, resulting in an increased uptake of LDL cholesterol from the blood and the subsequent lowering of circulating cholesterol levels (Baigent et al., 2005). In addition, statins have anti-inflammatory and antiproliferative effects (Kolyada et al., 2001). In some cases, statins produce characteristic alterations in liver histopathology (e.g. periportal hepatocellular atypia) (Kolyada et al., 2001).

As already stated, Alc’s oxidation may provoke oxidative stress, alter peroxisome proliferator activated receptor function (Huang et al., 1999) and induce potent inflammatory cytokines such as tumour necrosis factor-alpha (McCuskey et al., 1995). In contrast, statins increase nitric oxide production and/or bioavailability which may stabilize the hepatic microvascular inflammatory response to acute Alc ingestion, helping to protect the liver from ischemia and oxidative injury (Kolyada et al., 2001). Also, statins have been shown to suppress the secretion of tumour necrosis factor-alpha by monocytes (Okopien et al., 2005), a process probably applicable in the hepatic microvasculature. Therefore, statins may prove to be useful in patients with alcoholic hepatitis (Stickel et al., 2003) and even more useful in prevention before full alcoholic hepatitis is developed.

On the other hand, statins are metabolized by the microsomal ethanol-oxidising system (Blum, 1994), a system also used for Alc oxidation in the case of chronic consumption. It has been suggested that this fact possibly leads to statin enhanced metabolism by Alc administration often because of the induction of liver microsomal enzymes. (Bottorff and Hansten, 2000; Lieber, 2003) Statins’ oxidation is carried out mainly through cytochrome P450 3A4 and also through P450 2C9 and P450 2D6. In contrast, the most prominent cytochrome for Alc is P450 2E1, as already stated, while P450 3A4 is only a minor contributor to overall ethanol metabolism (Bottorff and Hansten, 2000; Lieber, 2003).
Acute and chronic effects of ethanol are usually opposite in the context of drug metabolism. In contrast to chronic use, an acute dose of ethanol inhibits the metabolism of drugs such as statins. Although this inhibition has been attributed, to some extent, to the competition for an at least partially shared microsomal detoxification pathway (Lieber, 1980), acute ethanol consumption mainly decrease drug metabolism indirectly by affecting the supply of NADPH (a cofactor necessary for the microsomal ethanol-oxidising pathway) through excess NADH production in the ADH pathway (Figure 2) (Thurman and Kauffman, 1979).

However, statin effectiveness was not affected in studies with concurrent chronic use of Alc. In contrast, Zdrenghea et al. (2004) observed that moderate Alc consumption in combination with simvastatin increased the beneficial effect upon HDL cholesterol, after comparing twenty patients on simvastatin monotherapy (20 mg per day) with twenty patients on the same dose of simvastatin plus 30 g of Alc per day for a two-week period. In addition, a substudy of WOSCOPS, showed that subjects who drank >21 units of Alc per week appeared to have smaller reductions in LDL at all ages and a smaller increase in HDL cholesterol in response to statin treatment (Streja et al., 2002). Smit et al. (1995) found that Alc ingestion of 20 g per day for 6 weeks together with fluvastatin (40 mg per day) resulted in greater total and LDL cholesterol reduction.

Concerning the safety of Alc and simvastatin chronic combination, in a study involving Wistar rats, no liver histopathological derangement was caused, while simvastatin decreased the Alc-induced TG and AST rises (Kolovou et al., 2003).

**Fibric Acid Derivatives**

Fibric acid derivatives (fibrates) lower plasma TG and raise HDL levels and thus are used to treat hypertriglyceridemia (Todd and Ward, 1988). Fibrates have a different mode of action than statins by reducing TG-rich lipoprotein precursors and favourably altering LDL and HDL composition (Scott, 1997). They also modulate thrombotic homeostasis in the blood (Catapano,
Fibrates bind to peroxisome proliferator-activated receptor-alpha, a nuclear receptor superfamily member, and induce beta-oxidation of fatty acids in mitochondria (Tsutsumi et al., 2001).

Due to this latter effect, there are studies evaluating fibrates in the treatment of alcoholic fatty liver. Alc metabolism causes accumulation of fatty acids in the liver and a concomitant rise in serum TG levels (Ginsberg et al., 1974). Tsutsumi et al. (2001) showed that hepatic TG content was significantly decreased in Alc-treated rats that were given fenofibrate. Hayashi et al. (2000), on the other hand suggested that simfibrate and clinofibrate induced beta-oxidation by peroxisome and increased H₂O₂ production, which led to augmented ethanol metabolism by catalase. This action of fibrates was also supported by Tsukamoto et al. (1996), who studied another fibrate, bezafibrate. However, fibrates can cause hepatotoxicity, hepatic peroxisome proliferation and cancer in rats (Sausen et al., 1995). Nevertheless, in combination with Alc consumption, fibrates were shown to be safe for the liver after histopathological assessment in rats (Kolovou et al., 2004).

Concerning humans, Tsutsumi et al. (2001) observed a decrease in serum TG and total cholesterol levels after treatment with fenofibrate in alcoholic patients, while no fibrate-induced hepatotoxicity has been reported in humans (Sausen et al., 1995).

**Nicotinic Acid**

Nicotinic acid (NA) lowers plasma total cholesterol and TG levels, reducing VLDL and LDL cholesterol levels, and is also effective in raising HDL cholesterol (Tatò et al., 1998). The plausible mechanism is that NA reduces the production of free fatty acids by inhibiting lipolysis in adipose tissue, which results in a reduced availability of substrate for VLDL synthesis in the liver (Tatò et al., 1998). This speculation was confirmed by the identification of a G-protein coupled receptor that is highly expressed in adipose tissue and to which NA is a high-affinity ligand (Wise et al., 2003). The binding of NA to its receptor activates a G-protein signal, which reduces cAMP.
concentrations and thus inhibits lipolysis. However, a “rebound” elevation in free fatty acids has been described (Karpe and Frayn 2004). Karpe and Frayn (2004) suggest that the effect of NA relies on the down regulation of the activity of hormone-sensitive lipase. The lowering of free fatty acid concentration results in a reduction in triglyceride levels, which in turn leads to increased HDL cholesterol. Another potential mechanism by which NA raises HDL cholesterol levels is through the stimulation of the ATP-binding cassette A1-mediated transfer of cholesterol (Rubic et al., 2004). It has also been suggested that NA directly inhibits the synthesis of apo B-containing lipoproteins in the liver (Tatò et al., 1998).

Since NA reduces the production of free fatty acids, it could be speculated that its administration may also protect against ethanol-induced fatty liver. Sorrell et al. (1976) reported that NA not only does not protect against the ethanol-induced fatty liver but that it potentiates steatosis in rats. They attributed their findings to the fact that, after chronic ethanol administration, the source of the accumulated TG in liver is dietary fatty acids and not those from adipose tissue (Sorrell et al., 1976). Therefore, the inhibition of adipose tissue lipolysis by NA did not protect against ethanol-induced fatty liver. However, in a study of ours involving rats, Alc-induced secondary hypertriglyceridemia was alleviated after NA administration (Kolovou et al., 2005). Inhibition of hepatic steatosis and alcohol dehydrogenase by NA in ethanol-treated rats was also reported by Baker et al. (1973). It has been suggested that NA interacts with Alc (Bays and Dujovne, 1998), but it was also shown that in experimental animals it may reduce Alc-induced aspartate aminotransferase rises (Kolovou et al., 2005).

The administration of NA though, can be accompanied by adverse effects in humans, which include flushing, itching, nausea, diarrhea, decreased glucose tolerance, hyperuricemia and hyperhomocysteinemia (Meyler, 1998). Raised hepatic enzymes, cholestasis and hepatocellular injury have also been reported after NA administration (Patterson et al., 1983). The tissue distribution of the NA receptor implies that the effects observed in the liver are secondary to
alterations in fatty acid metabolism (Karpe and Frayn, 2004). The evidence suggests that in humans, NA-induced toxicity is dose-related (Clementz 1987). However NA, in the range of recommended human dose, when co-administered with Alc in rats, did not disturb liver histopathology (Kolovou et al., 2005).

Conclusions

The beneficial or the detrimental effect of Alc on cardiovascular disease is explained by plausible physiological mechanisms. Light-to-moderate Alc consumption on a regular basis reduces cardiovascular risk without side effects; whereas irregular heavy drinking has a negative effect on all-cause mortality. It seems that all-cause mortality attributed to Alc is determined by both the pattern and the total volume of Alc intake (Rehm et al., 2003). An interesting aspect is that of population differences in Alc metabolic efficiency, which is likely to contribute to an individual's susceptibility to Alc-related diseases. Studying genetic differences that potentially influence disease susceptibility among populations may provide insight into the mechanism(s) for the relationship between risk factor and disease, such as Alc and CHD (Hines, 2004).

Patients at high CHD risk could gain from the beneficial effects of Alc. Since most of these patients are on lipid-lowering drugs, a question whether Alc drinking can be combined with hypolipidemic treatment arises. Attention should be paid in patients with alcoholic liver disease in which hepatic function is already disturbed and administration of lipid-lowering drugs may lead to aggravation of the existing disease. The prescription of hypolipidemic treatment to patients with chronic liver disease is under consideration, since little evidence exists concerning any further liver injury induced by such treatment. In cases where hypolipidemic therapy is required, the patients should be closely monitored. However, in patients with acute liver disease (acute viral hepatitis, alcoholic hepatitis) such drugs should not be administered until recovery (Russo and Jacobson, 2004).
More research is needed to determine whether the consumption of Alc in combination with hypolipidemic therapy should be recommended and if it is safe. Furthermore, there is a need to define the benefit and establish which drug behaves better in such a setting.
References


Legends for figures.

Figure 1. The mechanisms underlying the Alc-induced elevation of HDL cholesterol levels.

I) nascent HDL formation through enhanced hepatic synthesis of apo AI, II.
II) Overproduction of TG-rich lipoproteins, hyperactivity of TG lipases that leads to hydrolysis and free cholesterol eflux to pre-β-HDL particles.
III) Decreased TG and cholesteryl ester exchange through CETP inhibition and thus reduced HDL catabolism.


Figure 2. The pathways of alcohol catabolism.

Figure 1

I) Synthesis of apo A-I and apo A-II leads to an increase in pre-β-HDL.

II) Increased TG lipases cause an increase in mature HDL.

III) CETP activity decreases, leading to an increase in pre-β-HDL.

Legend:
- cholesteryl ester
- phospholipid
- triglyceride
- Free cholesterol

apoA, apoAI, apoAII, apoB100, apoC, apoE, apoB48, CM

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**ADH route**

- **Alc consumption:**
  - Moderate
  - Acute

**MEOS route**

- **Alc consumption:**
  - Chronic heavy
  - Acute

**Medications**

**Figure 2**

*Alcohol dehydrogenase*

- Alc
  - Alcohol dehydrogenase
  - NAD
  - NADH

*Aldehyde dehydrogenase*

- Acetaldehyde
  - NO

*CYP450 2E1*

- Acetate

*P450*

- Acetaldehyde
  - NADPH + O₂
  - ROS
  - NADP + H₂O

**P450 Variants**

- **CYP450 2E1**
  - Major role in Alc metabolism

- **CYP450 1A2**
  - Minor role in Alc breakdown

- **CYP450 3A4**
  - Minor role in Alc metabolism
  - Major role in statin metabolism

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