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Effects of Cigarette Smoking on HDL Quantity and Function: Implications for Atherosclerosis

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ABSTRACT

Cigarette smoking has been identified as an independent and preventable risk factor for atherosclerosis and cardiovascular disease. Population studies have shown that plasma high density lipoprotein (HDL) cholesterol levels are inversely related to the risk of developing cardiovascular disease. Cigarette smoking is associated with reduced HDL cholesterol levels. Cigarette smoking can alter the critical enzymes of lipid transport, lowering lecithin: cholesterol acyltransferase (LCAT) activity and altering cholesterol ester transfer protein (CETP) and hepatic lipase activity, which attributes to its impact on HDL metabolism and HDL subfractions distribution. In addition, HDL is susceptible to oxidative modifications by cigarette smoking, which makes HDL become dysfunctional and lose its atheroprotective properties in smokers. Therefore, cigarette smoking has a negative impact on both HDL quantity and function, which can explain, in part, the increased risk of cardiovascular disease in smokers. J. Cell. Biochem. 114: 2431–2436, 2013.

KEY WORDS: CIGARETTE SMOKING; HDL; ATHEROSCLEROSIS; HDL METABOLISM; HDL FUNCTION

Cigarette smoking has been identified as the second common cause of death in the world [Gu et al., 2009]. Numerous epidemiologic studies have demonstrated that cigarette smoking is an independent risk factor for atherosclerosis and coronary heart disease [Baldassarre et al., 2009; Kweon et al., 2012]. However, the mechanisms by which cigarette smoking increases the risk of cardiovascular disease are not completely clarified. Accumulating experimental and clinical data have indicated that endothelial dysfunction, platelet activation, increasing oxidative stress, inflammation as well as alterations in the lipid profile have been considered as the potential mechanisms of cigarette smoking increasing cardiovascular disease [Ambrose and Barua, 2004; Armani et al., 2009]. Recently, many studies showed that cigarette smoking disrupts lipid and lipoprotein metabolism. Smokers exhibit an elevation of plasma cholesterol, triglycerides, and low density lipoprotein (LDL) level, and a decrease in high density lipoprotein (HDL) cholesterol level, as compared with nonsmokers [Craig et al., 1989; Chelland Campbell et al., 2008; Tan et al., 2008]. In particular, the effect of cigarette smoking on HDL contributes to the increased risk of cardiovascular disease in smokers.

HDL has several potentially anti-atherogenic properties. These functions include cholesterol efflux and reverse cholesterol transport, anti-oxidative and anti-inflammatory activities [Soran et al., 2012]. Low levels of plasma HDL cholesterol are associated with an increased risk of cardiovascular disease [Singh et al., 2007; Bochem et al., 2012]. A meta-analysis of four prospective studies reveals that each 1 mg/dl decrease in plasma HDL cholesterol concentration is associated with a 2% (in men) or 3% (in women) increased risk of cardiovascular disease [Gordon et al., 1989]. Cigarette smoking exerts a negative effect on the level of HDL cholesterol, causing a 5.7% decrease in concentration [Craig et al., 1989]. And it also has been reported that smoking cessation leads to normalization of HDL cholesterol to values similar to nonsmokers. [Moffatt et al., 2000; Gepner et al., 2011]. In addition, HDL can be oxidatively modified by cigarette smoking, leading to dysfunctional HDL that could promote atherogenesis [Ueyama et al., 1998]. Therefore, the effects of cigarette smoking on HDL quantity and function may explain, in part, the increased risk of cardiovascular disease in smokers [Nakamura et al., 2009]. In this review, we will outline the effects of cigarette smoking on HDL quantity and function, which possibly play an

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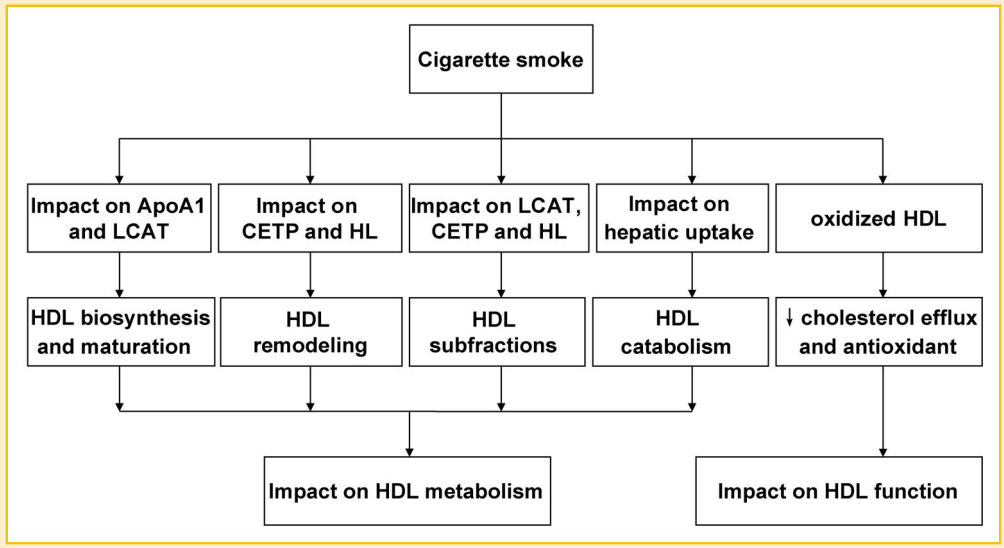

Fig. 1. Effects of cigarette smoking on HDL metabolism and function. Cigarette smoking impacts many steps of HDL metabolism, including HDL biosynthesis and maturation, intravascular remodeling of HDL, HDL subfractions and catabolism of HDL, which contributes to the decrease of HDL. In addition, HDL is susceptible to be oxidative modifications by cigarette smoking, consequently loses its atheroprotective properties and becomes dysfunctional or even atherogenic.

important role in the initiation and progression of atherosclerosis (Fig. 1).

CIGARETTE SMOKING ASSOCIATED WITH THE LOW HDL CHOLESTEROL LEVEL

Numerous studies have shown that there is an inverse association between cigarette smoking and HDL cholesterol [Nakamura et al., 2009]. The Lipid Research Clinics Program Prevalence Study [Criqui et al., 1980] examined 2,663 men and 2,553 women aged 20–69 in 10 North American populations to analyze the relationship between cigarette smoking and HDL cholesterol level, which found that both male and female smokers had significantly lower HDL cholesterol level than nonsmokers. For male smoker (20 or more cigarettes per day), HDL cholesterol level averaged 5.3 mg/dl (11%) lower than those of nonsmokers. For female smokers, HDL cholesterol level had 8.6 mg/dl (14%) lower than those of nonsmokers. A meta-analysis of 54 published studies by Craig et al. [1989] also showed a reduction (5.7%) of HDL cholesterol in smokers, as compared with nonsmokers. In addition, passive cigarette smoking also exerts a negative effect on the level of HDL cholesterol [Neufeld et al., 1997; Hirata et al., 2010]. These findings indicate that cigarette smoking is associated with reduced HDL cholesterol level.

The effect of cigarette smoking on HDL cholesterol levels is dose-dependent. Subjects smoking 1–19 cigarettes per day had HDL cholesterol levels intermediate between nonsmokers and subjects who smoked 20 or more cigarettes per day [Criqui et al., 1980]. As compared with nonsmokers, light, moderate and heavy smokers show a dose related reduction of HDL cholesterol (4.6%, 6.3%, 8.9% reduction, respectively) as the smoking dosage increased from light to heavy.

In contrast, smoking cessation has been reported to elevate HDL cholesterol level. The level of HDL cholesterol in ex-smokers is either the same as that found in nonsmokers or intermediate between smokers and nonsmoker [Garrison et al., 1978]. A meta-analysis derived from 24 studies by Maeda et al. [2003] resulted that the mean value of HDL cholesterol increased by 3.9 mg/dl after smoking cessation and the effect of smoking cessation on HDL cholesterol was expected to reduce the risk of coronary heart disease by 7.4–9.0% in men and 12.5% in women.

EFFECTS OF CIGARETTE SMOKING ON HDL METABOLISM

Although cigarette smoking is associated with reduced HDL cholesterol levels, the mechanisms have not been fully elucidated. Accumulating studies suggest that the effects of cigarette smoking lowering HDL cholesterol may attribute to its influence on the process of HDL metabolism. The process of HDL metabolism is complex, which consists of three main steps: HDL biosynthesis and maturation, intravascular remodeling of HDL, catabolism of HDL [Lewis and Rader, 2005; Rader, 2006; Leiva et al., 2011]. A number of enzymes and transfer proteins play key roles in the process of HDL metabolism, in which all steps can be affected by cigarette smoking.

EFFECTS OF CIGARETTE SMOKING ON HDL BIOSYNTHESIS AND MATURATION

HDL biosynthesis is complex and involves the synthesis and secretion of lipid-poor apolipoprotein A-I (apoA-I) followed by acquisition of cholesterol and phospholipids from the liver to form nascent HDL particles [Zannis et al., 2006]. ApoA-I constituting approximately 70% of HDL protein is required for HDL biosynthesis. Human subjects with apoA-I deficiency and apoA-I deficient mice fail to form normal HDL particles [Williamson et al., 1992; Rashid et al., 2009]. Cigarette smoking can decrease the level of apoA-I. In a study of 315 men and

women from Iceland, the mean levels of apoA-I in smokers were 6% lower compared with nonsmokers [Sigurdsson et al., 1992]. In addition, one study showed that apoA-I concentration returned to the concentration in nonsmokers in the process of quitting smoking [Richard et al., 1997]. These effects may attribute to the reduction of apoA-I synthesis in smokers [Naem et al., 2012].

Nascent HDL particles acquire additional free cholesterol from extrahepatic tissues and this free cholesterol is then esterified to cholesteryl ester by lecithin: cholesterol acyltransferase (LCAT), contributing to generate small spherical HDL3 and in turn large spherical HDL2, the latter of which can then be converted to HDL3 [Rader, 2006]. LCAT is critical for the maintenance of normal HDL metabolism. LCAT deficiency in humans [Kuivenhoven et al., 1997] and in mice [Ng, 2004] cause markedly reduced levels of HDL cholesterol and rapid catabolism of apoA-I and apoA-II [Rader et al., 1994]. Numerous studies have reported that smokers had significantly lower plasma LCAT concentrations or activity than nonsmokers [Imamura et al., 2002]. McCall et al. [1994] studied the effect of cigarette smoke on LCAT activity. Freshly isolated plasma (24 ml) was exposed to filtered air or gas phase cigarette smoke for up to 6 h at 37°C. Within 1 h the cigarette smoke exposed plasma had a 44% reduction in LCAT activity, and the longer the plasma was exposed to cigarette smoke the greater the decrease in activity. After 6 h, only 22% of control LCAT activity remained in plasma exposed to cigarette smoke. The effect of cigarette smoke on LCAT activity may impair the maturation of HDL, which in turn leads to a rapid clearance of nascent HDL from the circulation. Therefore, the change of LCAT activity is a possible mechanism by which HDL cholesterol level is reduced in smokers.

EFFECTS OF CIGARETTE SMOKING ON INTRAVASCULAR REMODELING OF HDL

Intravascular remodeling of HDL particles is an important determinant of the rate of HDL clearance from the circulation, which includes lipid exchange and lipolytic modification. A number of lipid transfer factors and lipolytic enzymes play key roles in this process. Cholesterol ester transfer protein (CETP) facilitates the exchange of cholesteryl ester in HDL for triglycerides in apolipoprotein B containing and triglyceride-rich lipoproteins such as LDL and VLDL. The exchange of cholesterol ester and triglyceride mediated by CETP not only leads to depletion of cholesteryl ester and enrichment with triglycerides in HDL, but also decreases the levels of HDL cholesterol [Barter et al., 2003; Barkowski and Frishman, 2008]. Some studies have shown that CETP activity is elevated in smokers. Dullart et al. [1995] studied the effect of cigarette smoking on CETP activity, which demonstrated that plasma CETP activity was 18% higher in the smokers than that in the nonsmokers. Multiple regression analysis showed that the lowering effect of cigarette smoking on HDL cholesteryl ester could be explained by its influence on CETP activity. However, Freeman reported that cigarette smoking had no effect on CETP activity [Freeman et al., 1998]. The varied results may result from the different methodology in the two studies. Therefore, the effect of cigarette smoking on CETP activity needs further study.

Hepatic lipase is a lipolytic enzyme which can catalyze hydrolysis of HDL triglycerides as well as HDL phospholipids. Consequent to it, hepatic lipase has an inverse relationship to HDL cholesterol concentration [Rye et al., 1999] and is involved in the generation of HDL_3 from HDL_2 [Jin et al., 2002]. Kong studied the effect of cigarette smoking on hepatic lipase activity and HDL cholesterol level in type 2 diabetic subjects and found that smokers had lower HDL and HDL_2 cholesterol levels and increased hepatic lipase activity [Kong et al., 2001]. For further analysis, they confirmed that there was an inverse relationship between hepatic lipase activity and both HDL and HDL_2 cholesterol levels. However, the effect of cigarette smoking on hepatic lipase activity is controversial. Zaratin et al. [2004] reported that normolipidemic smokers presented 30% lower hepatic lipase activity as compared with nonsmokers, which prevented the intravascular remodeling of HDL particles and impaired reverse cholesterol transport. The converse results may attribute to the different populations in the two studies, which also needs further study.

EFFECTS OF CIGARETTE SMOKING ON HDL SUBFRACTIONS

Interconversion of HDL_3 and HDL_2 can occur in the arterial wall and in plasma in the process of HDL metabolism, which is mediated by LCAT, CETP, and hepatic lipase [Rye et al., 2009]. LCAT can converts lipid-poor pre-β-HDL to HDL_3 and subsequently to HDL_2, thereby generating large HDL_2. CETP redistributes cholesteryl ester from HDL to apoB-lipoproteins and remodels HDL into small particles, which leads to decrease in the numbers of large HDL_2 particles. Conversely, the smaller, denser HDL_3 subfraction is formed when HDL_2 particles are hydrolyzed by the enzyme hepatic lipase.

Cigarette smoking has an impact on the process of HDL metabolism and therefore may affect the distribution of HDL subfractions. Several studies have shown that smoking mainly reduces the HDL_2 subfraction [Moriguchi et al., 1991; Freeman et al., 1993], however there is little change of HDL_3 due to smoking or cessation from smoking. Imamura et al. [2002] examined the relationship of cigarette smoking with HDL subfractions and LCAT activity in Japanese collegiate women. They found that the smokers had significantly lower HDL levels, HDL_2 levels and LCAT activity than the nonsmokers. The lower HDL levels in smokers had been attributed to the reduced HDL_2. In addition, secondhand smoke can also decrease HDL_2 levels. Women exposed to secondhand smoke at work at least 6 h per day for 6 consecutive months had HDL_2 levels significantly lower than those of nonsmokers [Moffatt et al., 1995]. The effect of passive smoking on HDL_2 was similar to active smokers.

EFFECTS OF CIGARETTE SMOKING ON HDL CATABOLISM

HDL plays a key role in the regulation of cholesterol balance by transporting excess cholesterol from peripheral cells and delivering to the liver and steroidogenic cells for catabolism. The major site of HDL cholesterol uptake is the liver. Cigarette smoking can impair hepatic uptake of HDL cholesterol. Mulligan et al. [1983] investigated the effect of chronic inhalation of cigarette smoke on hepatic uptake of HDL in White Carneau pigeons. Liver from pigeons exposed to cigarette smoke had less HDL ^{3}H-cholesterol and HDL ^{14}C-apoprotein than that exposed to fresh air. It indicates that cigarette smoking impairs hepatic uptake of HDL, which may be one of the mechanisms related to the effects of cigarette smoking attenuating HDL anti-atherogenic properties.

EFFECTS OF CIGARETTE SMOKING ON HDL FUNCTION

HDL exerts its protective effects through several putative mechanisms, including reverse cholesterol transport, antioxidant, anti-inflammatory, and vasoprotective properties [Fisher et al., 2012]. However, accumulating studies indicate that HDL does not always have an atheroprotective properties [Ferretti et al., 2006; Ansell et al., 2007; Feng and Li, 2009; de la Llera Moya et al., 2012]. HDL can be modified and become dysfunctional in certain circumstances.

IMPAIRED HDL ATHEROPROTECTIVE PROPERTIES BY OXIDATIVE MODIFICATIONS

Recent data have demonstrated that HDL is susceptible to oxidative modifications by a variety of oxidants such as metal ions, lipoxygenase [Pirillo et al., 2008], myeloperoxidase [Undurti et al., 2009], peroxyl and hydroxyl radicals [Bowry et al., 1992], peroxidase-generated tyrosil radical and cigarette smoking [McCall et al., 1994; Ueyama et al., 1998]. The formation of lipid peroxidation derivatives, such as thiobarbituric acid reactive substances, lipid hydroperoxides and aldehydes, are associated with changes of HDL conformation and physiological properties [Garner et al., 1998]. Strong evidence exists to suggest that these oxidative modifications of HDL can lose its atheroprotective properties. Oxidized HDL has been detected in the intima of atheromatous plaques which increases with the severity of disease [Nakajima et al., 2000]. And these oxidized HDL can impede reverse cholesterol transport, enhance oxidation of LDL and increase vascular inflammation, which consequently becomes dysfunctional or even atherogenic.

EFFECTS OF CIGARETTE SMOKING ON LIPID PEROXIDATION

Tobacco smoke contains large numbers of gas, tar phase radicals, and other oxidants which can induce oxidative stress. It has been estimated that a single puff of a cigarette contains as much as 10^{15} gas phase radicals and 10^{14} tar phase radicals potentially capable of modifying endogenous macromolecules including lipids [Rahman and Macnee, 1996]. Therefore, cigarette smoking increases oxidative stress as a potential mechanism for initiating cardiovascular disease, leading remarkably to lipid peroxidation. Accumulating studies have shown that LDL isolated from smokers is more susceptible to oxidation than that from nonsmokers [Morrow et al., 1995; Isik et al., 2007]. Furthermore, levels of oxidized LDL are higher in smokers than in nonsmokers.

EFFECTS OF CIGARETTE SMOKING ON OXIDATIVE MODIFICATION OF HDL

Accumulating data have shown that HDL is susceptible to be modified by cigarette smoking. Ueyama et al. [1998] incubated HDL with the cigarette smoke extract and found that the level of lipid peroxidation increased. In addition, the apolipoprotein composition of HDL is susceptible to oxidative modifications by cigarette smoking. McCall et al. [1994] investigated the direct effects of gas-phase cigarette smoke on plasma and found that exposing to cigarette smoke for 6 h showed a 12% increase in agarose-gel mobility of HDL, which suggested that HDL is easy to be oxidatively modified by cigarette smoking. Cigarette smoking can oxidatively modify HDL not only through the production of reactive oxygen radicals in smoke but also through weakening the antioxidant enzymes in HDL. Paraoxonase is tightly linked to HDL and is a HDL associated enzyme with antioxidant function, which can protect lipoproteins from oxidative modifications. Cigarette smoking has a negative impact on serum paraoxonase activity and concentration. James et al. [2000] found that cigarette smoking was independently associated with significant decrease in serum paraoxonase activities and concentrations, which normalized within a relatively short time of cessation. These results demonstrate that cigarette smoke inhibits the enzymatic activity of paraoxonase.

EFFECTS OF CIGARETTE SMOKING ON DYSFUNCTION OF HDL

Available data have shown that HDL is susceptible to be modified by cigarette smoking. Ueyama et al. [1998] studied the effect of cigarette smoking on HDL function. They prepared cigarette smoke extracts treated HDL (CS-HDL) by incubating HDL with whole cigarette smoke extracts and examined its effect on cholesterol efflux. The cholesterol efflux activity of CS-HDL was remarkably reduced to the same level as that of oxidatively modified HDL induced by copper ion. Addition of 20 mg/ml superoxide dismutase (SOD) during the cigarette smoke extracts modification of HDL caused retrieval of cholesterol efflux activity by 53%. These results demonstrate that the cholesterol efflux activity of CS-HDL is impaired and that lipid peroxidation associated with superoxide anion is involved in this functional impairment. Therefore, cigarette smoking has a negative impact on the anti-atherogenic properties of HDL, which attributes to the increased risk of cardiovascular disease in smokers.

CONCLUSION

The relationship between cigarette smoking and the increased cardiovascular disease has been well established in numerous epidemiologic studies and basic studies. The effects of cigarette smoking on lipid and lipoprotein metabolism, in particular the impact on HDL, contribute to its deleterious effects on cardiovascular disease. Cigarette smoking exerts a negative effect on HDL cholesterol, causing a 5.7% decrease in concentration. The mechanisms of cigarette smoking lowering HDL cholesterol may partly attribute to affect the process of HDL metabolism. In addition, HDL can be modified by cigarette smoking, which could lead to lose its protective properties or even become atherogenic. Therefore, the effects of cigarette smoking on HDL quantity and function may explain, in part, the increased risk of cardiovascular disease in the smokers (Fig. 1).

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