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Review

Smoking and smoking cessation—The relationship between cardiovascular disease and lipoprotein metabolism: A review

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Abstract

Cigarette smoking is generally accepted as the most preventable cause of death in the United States today. Individuals who smoke experience a wide range of physiologic side effects that increase the risk of cardiovascular disease (CVD), including insulin resistance, elevated catecholamine levels which contribute to an elevated heart rate and blood pressure, and hypercholesterolemia.

The link between hypercholesterolemia and cardiovascular disease has been extensively researched and is undeniable. What is more, this link is strengthened in smokers as cigarette smoking is known to increase total cholesterol (TC), triglycerides (TG), and low-density lipoprotein (LDL), while acting to decrease the cardio-protective high-density lipoprotein (HDL). Alterations in the enzymes that control lipid transport may be a key underlying mechanism contributing to these health destroying effects.

This review examines the current literature related to: (1) smoking, lipoproteins, and lipid-related enzymes; (2) the impact of nicotine, carbon monoxide and free radicals on physiologic parameters related to health; and (3) metabolic issues involving smoking cessation and nicotine replacement therapy.

Keywords: Cigarette smoking; Lipids; Lipoproteins; Lipid-transport enzymes; Cardiovascular disease; Nicotine; Metabolism; Carbon monoxide

Contents

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1. Introduction

Cardiovascular disease (CVD) is the leading cause of mortality and morbidity in the U.S. [1]. CVD is promoted by non-modifiable risk factors (genetic predisposition to the disease, age, and gender), as well as those that can be modified by lifestyle intervention. These include obesity, hypertension, hypercholesterolemia, diabetes, lack of physical activity and cigarette smoking.

Trends within the past 15 years suggest that every year since 1991 the prevalence of modifiable risk factors has increased and is reflected in the number of individuals who refrain from physical activity [2] and who are classified as obese [3]. Moreover, the incidence of individuals who start smoking is on the rise again after a noticeable drop, and this is particularly prevalent among children, especially students in the 8th, 10th, and 12th grades [4].

Atherosclerosis, the underlying cause of CVD, is greatly enhanced by abnormal plasma lipid and lipoprotein profiles. Such profiles are characterized in the Third Report of the National Cholesterol Education Program [5] as demonstrating one or more of the following:

- low-density lipoprotein (LDL) > 100 mg/dL;
- triglyceride (TG) > 200 mg/dL;
- total cholesterol (TC) > 200 mg/dL;
- high-density lipoprotein (HDL) < 40 mg/dL.

Individuals are placed into risk categories based on LDL measurements and identification of accompanying risk determinants, including smoking, hypertension, low HDL, family history and age [5]. The health destroying impact of lipoprotein abnormalities escalates markedly when combined with cigarette smoking. What is more, smoking exacerbates the degree of lipoprotein abnormality, thus contributing in a sense to a deadly spiraling effect. The purpose of this review was to examine the impact of cigarette smoking on lipoprotein metabolism and related issues.

2. CVD and cholesterol

Several large cohort studies have examined the effects of modifiable risk factors on CVD. The Framingham, Oslo, Helsinki, and Bogalusa Heart Studies as well as the Multiple Risk Factor Intervention Trials (MRFIT) were all designed to examine the etiology of CVD and, perhaps more important, how to reduce its prevalence [6–10].

The Framingham Heart Study initiated in 1948 was among the first to reveal a relationship between the incidence of atherosclerosis and higher blood cholesterol levels [11]. Subsequent studies focused on the combined impact of blood cholesterol and other risk factors. The MRFIT studies, for example, reported an independent contribution to increased mortality for elevated cholesterol as well as a substantial escalation in risk arising from the combined influence of elevated cholesterol and cigarette smoking [10]. Similar results were reported in other epidemiological studies of varying populations [8,9,12].

Evolving data from the ongoing Framingham Heart Study revealed that blood lipoprotein concentration is a strong predictor of mortality arising from CVD [13]. Additional evidence supporting the connection between HDL and CVD was put forth in the 1970s by the Framingham, Tromoso and Honolulu Heart Studies [14–16]. Kostner [17] examined the various classes of lipoproteins and their contribution to CVD and reported three important findings. First, LDL had the strongest correlation to CVD mortality; second, there is an association between very low-density lipoprotein (VLDL) and CVD mortality (but it was not as strong as the relationship with LDL); and, third, HDL is a protective particle inversely related to CVD.

3. CVD and cigarette smoking

Cigarette advertisements were seen as early as 1913 and specifically targeted women, coaxing them to smoke rather than indulge in satisfying their sweet tooth. From there the surge of advertising was immense, especially during World War I and the Great Depression. Cigarettes had become more "palatable" as the former harsh tobaccos from Turkey were being replaced with milder brands. Smoking rates accelerated during the War as cigarettes were easier to manage than a pipe, and the government provided daily rations of cigarettes to soldiers free of charge. The rate of smoking continued to accelerate, peaking at approximately 53.5 million people in 1983 [18].

Quit smoking campaigns have had a transient impact on the incidence of smoking. Today, it is estimated that 25.5 million American men (24.1%) and 21.5 million American women (19.2%) smoke cigarettes [19]. Tens of millions continue to smoke even though smoking is directly responsible for as many as 465,000 deaths per year divided among CVD (201,000), lung cancer (112,000), chronic lung disease (83,000), other cigarette-related cancers (31,000) and environmental tobacco smoke (37,000) [2].

Knowledge of the health-destroying and potentially lethal impact of cigarette smoking is not new. As early as 1889, a French physician named Henri Huchard commented on the potential mechanisms of smoking on the spastic and sclerotic events associated with the coronary arteries [20]. Almost 50 years after Huchard and 20 years after smoking advertisements began Lewis published a paper suggesting an increased prevalence of CVD due to smoking [21]. The results of this paper indicted smoking as a contributing factor in the degeneration of the arteries, including the coronary arteries [21]. Years later, in 1950, Boston cardiologist, Samuel Levine, published a book providing evidence that death from coronary artery disease occurred prematurely in smokers compared to non-smokers [22]. Levine labeled cigarette smoking a major risk factor for acute myocardial infarctions.

Additional crucial evidence was published in 1958 when it was reported that men who smoked 20 cigarettes per day had twice the death rate due to coronary events than non-smokers [23]. Later, these same authors found that those men who stopped smoking decreased their mortality rate during a 12-year follow up [23]. In an earlier study, Doll and Hill [24] reported that the rate of death due to CVD decreased as individuals stopped smoking.

Since these early studies there has been considerable research focused on the physiologic consequences of smoking, the morbidity and mortality rates attributable to smoking, and the benefits accrued from smoking cessation. One such study is a 50-year follow up report based on the original Doll and Hill publication [24]. Doll et al. [25] concluded that the substantial decrease in mortality rate among non-smokers, due to prevention and treatment, has been outweighed among smokers because of progressive increase in death rate due to earlier and more intensive use of cigarettes. A devastating outcome of smoking, among many, is the negative impact on lipoprotein metabolism. This may explain, at least in part, the prevalence of both smoking and abnormal lipoprotein status in this country. In turn, this combination substantially increases the risk of CVD.

4. Cigarette smoking impacts lipids and lipoproteins

A comprehensive meta-analysis by Craig et al. [26] examined published data from 1966 to 1987 and estimated the excess risk posed by smoking on CVD, with particular emphasis on lipid and lipoprotein involvement. Results of their analysis indicated that individuals who smoked cigarettes when compared with non-smokers had significantly higher TC (3%), TG (9.1%), and VLDL (10.4%), higher (but not significant LDL (1.7%), and lower concentrations of HDL (−5.7%) and apolipoprotein AI (Apo A-I) (−4.2%). Further analysis indicated a dose–response relationship between the number of cigarettes smoked per day and the extent of lipid and lipoprotein abnormalities.

A study by Law et al. [27] suggested that smoking 20 or more cigarettes per day elevated the relative risk for CVD by a factor of 1.78. Thus, cigarette smoking may increase the rate of CVD to a greater extent than can be explained by the impact of smoking on serum lipids and lipoproteins. This point was raised by McGill [28] who concluded that the small increase in risk for atherosclerosis due to smoking is not a sufficient explanation to account for the large (twofold) increase in myocardial infarction among smokers. Subsequent studies have shown that HDL, the major cardioprotective lipoprotein, is significantly reduced in smokers, which can alter cholesterol clearance via reverse cholesterol transport [29–31]. Moreover, cigarette smoking contributes to central adiposity and insulin resistance, which can alter the lipid and lipoprotein profile by interfering with fat metabolism [32–34].

5. Cigarette smoking and lipid metabolism

Cigarette smoking is detrimental to health and contributes to CVD via alterations in the lipid profile, and in particular the impact on HDL. One popular explanation is that cigarette particulate matter alters catecholamine release—and thus free fatty acid release, which in turn affects VLDL and LDL concentrations to favor their accumulation in the blood, contributing to a lower HDL concentration [35]. Ultimately cigarette smoking seriously disrupts lipid and lipoprotein metabolism, promoting atherogenesis.

Chronic cigarette smokers have a perturbed TG metabolism especially at the site of the adipose tissue. Chajek-Shaul et al. [36] compared the lipid content of adipocytes in the gluteal region of smokers and non-smokers of the same BMI. Smokers had significantly less lipid per cell than non-smokers (0.48 ± 0.07 μL/cell vs. 0.64 ± 0.16 μL/cell), and the authors suggested a difference in metabolism between smokers and non-smokers. A later study by Hellerstein et al. [37] examined the relationship between the thermogenic and atherogenic potential of cigarette smoke (CS). They examined heavy smokers ($n = 7$, serum cotinine $>309 \pm 40$ ng/mL during CS phase and <10 ng/mL during non-CS phase, >20 cigarettes per day) on a strict diet for 2 weeks, 1 week exposed to cigarette smoke and 1 week free from exposure. Stable isotope diffusions were used to measure free fatty acid (FFA) flux, glycerol flux and serum FFA concentrations associated with exposure to cigarette smoking. The plasma FFA concentration was increased 73%, and FFA flux increased by 77%. A concurrent increase in glycerol was noted and there was a threefold increase in hepatic esterification of FFA. These results suggest that cigarette smoking can contribute to VLDL formation and release, and thus provide a metabolic mechanism for atherogenesis.

TG metabolism is regulated by the action of lipoprotein lipase (LPL), an enzyme also affected by smoking. This enzyme is responsible for catalyzing TG hydrolysis and clearing TG from the blood. LPL is stimulated by insulin at the adipose tissue but suppressed by it at the muscular level. Research suggests that LPL activity at the skeletal muscle is reduced in smokers compared to non-smokers [36,38]. In contrast, however, adipose LPL activity does not appear to differ between smokers and non-smokers [29,33].

LPL activity at the skeletal muscle provides a greater lipid clearance than at the adipose tissue, therefore an altered activity at the musculature is of great importance. A study by Freeman et al. [38] examined 20 subjects, 10 non-smokers and 10 individuals who smoked at least 10 cigarettes per day. They matched each subject for age, height, weight and body mass index. Smokers were encouraged to maintain their normal smoking habits until 30 min prior to blood sampling when they were asked to abstain. Results revealed a trend for lower HDL-C levels in the smokers as well as higher TG, LDL and TC levels.

Results of the lipid transport enzymes demonstrated a significant ($P < 0.005$) decrease (33%) in skeletal muscle LPL activity in smokers (3.89 ± 1.58 μmol FFA mL^{-1} h^{-1}) compared to non-smokers (5.85 ± 2.30 μmol FFA mL^{-1} h^{-1}). The authors concluded that reduced LPL activity may explain the impaired TG clearance commonly seen in smokers due to a slower metabolism of the TG-rich lipoproteins, namely chylomicrons and VLDL. This perturbation may, in turn, decrease the recognition of surface material by the HDL particle and further delay cholesterol clearance.

LPL activity at the skeletal muscle is affected by insulin, and several studies have confirmed insulin resistance among smokers [32,33,39]. Results from Chajek-Shaul et al. [36] found an inverse relationship between the amount of insulin released and the amount of LPL activity, therefore those with the greatest insulin release showed the greatest fall in LPL activity. Eliasson et al. [33] suggested that the amount of insulin released is positively correlated to the amount of nicotine consumed per day. Thus, cigarette smoking can create an environment that causes constant stimulation of the sympathetic nervous system and release of catecholamines, which promotes the release of fatty acids. Ultimately this physiologic response should stimulate LPL. However, since LPL release is not stimulated, circulating TG concentration is increased. This perturbation can cause increased VLDL formation via both the decrease in LPL and insulin resistance.

The formation of excess VLDL is important because it provides the precursor for LDL formation, a major risk factor for CVD. However, LDL appears to be the least affected lipoprotein by smokers, increasing on average only 1.7%, according to Craig et al. [26]. The major concern regarding the impact of smoking on LDL has been the change in size to a smaller denser particle that can easily cross the endothelial barrier, lodging in the arterial intima [40]. Campos et al. [41] found that plasma TG concentrations are related to LDL particle size and HDL concentrations. Support for this claim comes from Griffin et al. [42] who observed a lower ratio of large to small LDL particles in smokers (LDL-I/III = 0.77) compared to non-smokers (LDL-I/III = 1.89). This disturbance was not found when corrected for TG, further suggesting that the altered TG metabolism directly influences the size and nature of the LDL particle.

A second concern with smoking and LDL is the propensity of LDL to oxidize and facilitate an immune response after it has been lodged in the arterial intima. This immune response will attract macrophages, initiating foam cell formation, the beginning stage of atherosclerotic plaque development. Smoking helps to initiate this process by the abundant free radicals found in smoke. One puff of a 30 mL cigarette contains 70 billion particles [43] rich in free radicals that cause lipid peroxidation. Altered lipid particles subject smokers to increased oxidative stress, as shown by an elevated TBARS concentration in smokers compared to non-smokers [44].

6. Cigarette smoking, HDL, subfractions and enzymes

Cigarette smoking exerts a negative effect on HDL, causing a 5.7% decrease in concentration. This would impede reverse cholesterol transport, a process that removes excess cholesterol from the blood and transports it to the liver for catabolism [26]. HDL works in concert with three key enzymes:

Lecithin cholesterol acyl-transferase (LCAT) esterifies free cholesterol in the presence of ApoA-I and promotes the movement of esterified cholesterol into the HDL core.

Cholesterol ester transfer protein (CETP) transfers esterified cholesterol from HDL to lower density particles (chylomicrons, VLDL, IDL, LDL).

Hepatic lipase (HL) is responsible for regulating the degradation rate of HDL at the liver.

When discussing HDL, it is important to comment its two subfractions, HDL_2 and HDL_3. HDL_2-C is the larger phospholipid-rich particle ranging from 8.8 to 13 nm whereas the HDL_3-C particles are smaller ranging from 7.3 to 8.7 nm. The HDL particles are negatively correlated to CVD—that is, the lower the concentration of HDL, the greater the degree of atherogenesis. This is because Apo A-I interacts with serum phospholipids and forms the nascent discoidial HDL (ndHDL). Once this ndHDL is formed this catalyzes cholesterol efflux in the macrophages and fibroblasts which is then absorbed by the ndHDL and subsequently esterified by LCAT. The HDL particle becomes enriched with cholesterol ester and gradually become larger making the HDL_3 and HDL_2 particles [45]. Smoking reduces the HDL_2 subfraction [29,30,46] while there is little evidence to support HDL_3 changes due to smoking [47] or cessation from smoking [48].

McCall et al. [31] analyzed LCAT and HDL response to cigarette smoke exposure via analysis of plasma samples obtained from non-smoking volunteers. The samples were exposed to one cigarette (Kentucky 2R1 research cigarettes with Cambridge filter) every 2 h for a total of 6 h. Analyses were made every 15 min to monitor precise changes in activity. Within 1-h the 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 LCAT activity was only 22% of the normal control. In addition HDL apolipoproteins were cross-linking rapidly (within 1 h) after exposure to smoke. In other words, Apo A-I, which is responsible for activating LCAT, was switching with apolipoprotein A-II (Apo A-II), known to inactivate LCAT. This is a major problem, because the activity of LCAT is dependent upon the activation by Apo A-I and furthermore governs cholesterol ester flow into the HDL core. This process "fattens" the HDL making it the larger HDL_2 particle, which can carry the cholesterol to the liver for excretion and/or catabolism.

McCall et al. [31] suggested that this study demonstrated how sensitive LCAT is to cigarette smoke and that this could

be directly responsible for the changes seen in HDL-C in smokers. The limitation to this study is that they used plasma of non-smokers. It would be interesting to observe changes that occur to a smoker's plasma when exposed to the same stimulus. It should be noted that several other studies have shown that Apo A-I concentration is 4.2% lower in smokers than non-smokers [26,47,49].

The enzymes LCAT, CETP and HL work to keep adequate levels of HDL in circulation so as to promote accumulation of esterified cholesterol. Studies have shown that smoking can both increase [29,34,113], and decrease the activity of HL [50] as well as inhibit the activity of LCAT [29,31,38,47]. The evidence on CETP is equivocal. It has been shown that CETP activity is elevated in smokers [51], while others report that it is decreased [30]; Zaratine et al., 2004 and still others report no change in activity [38]. Despite varied results, correlation analysis supports a strong negative relationship between total HDL-C, and HDL_2-C and HL. Furthermore, HDL_3-C was negatively correlated with LCAT [38]. These data suggest that these enzymes are directly responsible for maintaining the balance of HDL-C in metabolism, and that minor disruptions in the activity of these enzymes will have larger consequences.

The task now is to ascertain what all of these interactions have in common and how smoking augments the risk for CVD. What is known is that HDL-C will influence CVD risk and that LCAT aids in the essential process of reverse cholesterol transport (RCT). Deficiencies in LCAT have been shown to influence the concentration of HDL and hence can again be tied to an increase risk for CVD [52]. The reverse process of taking cholesterol esters away from the HDL-C in exchange for TG is mediated by CETP. In addition, HL will act on the HDL_2-C particles and return a smaller HDL to circulation.

Smoking reduces HDL_2-C and LCAT [29,31,38,47] two important players in RCT, both shown to be influential in CVD. Furthermore, the alterations in the activities of both CETP and HL [30,34,50,51,113] suggest that an individual will be at greater risk of CVD due to the disruption of cholesterol clearance by RCT. Finally, this combination of events may lead to an increase in the availability of substrate that could be incorporated into other less dense particles (VLDL, LDL).

7. Dose–response relationship between smoking and lipoproteins

In the meta-analysis conducted by Craig et al. [26], they compared non-smokers, to light, moderate, and heavy smokers and found a dose–response relationship between the number of cigarettes smoked and the change in lipid or lipoprotein variable. Their results indicated a progressive increase (%) as the smoking dosage increased from none to heavy: TC (0, +0.8, +4.3 and +4.5%), TG (0, +10.7, +11.5 and +18.0%), VLDL (0, +7.2, +44.4, and +39.0%), and LDL (0, −1.1, −1.4 and +11.0%). They also reported dose related decreases in HDL (0, −4.6, −6.3, −8.9%).

Other studies from the Lipids Research Clinic and Framingham [12,53] have shown a dose–response relationship between the number of cigarettes smoked and the decline in HDL concentration. The Lipids Research Clinic study [12] reported a substantial difference between smokers and non-smokers in the range of 0.06–0.22 mmol/L and that this difference was among both light (≤19 cigarettes per day) and heavy (≥19 cigarettes per day) smokers. This decrease in HDL would alter the LDL/HDL ratio to favor a more atherogenic profile. Freeman et al. [30] found a significant mean difference in the LDL/HDL ratio when comparing smokers (2.89 ± 1.18) and non-smokers (2.38 ± 0.98). The same study also reported that 40% of their smoking subjects demonstrated a LDL/HDL ratio of >4, placing them in a high-risk category. This negative change in the LDL/HDL ratio associated with cigarette smoking has been shown in several study populations [54–57].

8. Beyond the lipid profile

Although the focus of this review is on the influence of smoking on lipids and lipoproteins, it would be remiss to report that physiological perturbations as a result of smoking are limited to the lipid profile. Other mechanisms affected by cigarette smoke may also contribute to accelerating atherosclerotic lesion formation such as vasomotor and platelet dysfunction, inflammation, alterations in fibrinolysis, antithrombotic and prothrombotic factors. These are integral parts for both the initiation and progression of atherosclerosis and precede the clinical manifestations of the disease. Smoking exerts these health destroying effects largely through the influence of nicotine and carbon monoxide.

Nicotine is readily able to cross the blood–brain barrier and can bind to various receptors, causing release of acetlycholine, norepinephrine, dopamine, serotonin, and vasopressin [35]. These agents promote sympathetic stimulation and vasoconstriction of the arteries, which can elevate heart rate and blood pressure. Nicotine has a half-life of approximately 2 h, suggesting that a chronic heavy smoker (>19 cigarettes per day) may experience these elevations during at least part of their sleep cycle [35]. While the literature on nicotine supports this role of adversely affecting cardiac output and its related components, its role in atherosclerosis remains controversial. Studies have reported that nicotine alone has caused no change, a decrease or increase in nitric oxide (NO) [58–61]; and that levels commonly found in a smoker has only a minor effect on initiating or proliferating lesion formation [61,62].

The carbon monoxide in cigarette smoke contributes directly to coronary hypoxia, which manifests itself in changes that occur to the concentration of 2,3-diphosphoglycerate (2,3-DPG), an important modulator of hemoglobin's affinity for oxygen [63]. The concentration of

2,3-DPG is elevated in the blood of smokers signifying the body's attempt to compensate for the hypoxic environment created by carbon monoxide [63]. More recent data has however suggested that its role in atherosclerosis is equivocal [64] and an unlikely cause for atherosclerosis and thrombus [65–67].

Smoking increases the risk for major coronary events such as arterial thrombosis, myocardial infarction, and peripheral artery disease. These conditions can be linked to the function of the endothelial wall. The endothelial wall is made up of a single layer of endothelial cells that regulate blood circulation and metabolism of the vessel. As early as Mustard and Packham [68] listed carbon monoxide among those factors having the greatest impact on endothelial function. This is an important consideration, as Ross [69,70] has suggested that injury to endothelial cells is a critical step in initiating the atherosclerotic process. Waters et al. [71] concluded that smoking will accelerate production of new lesions in the arteries.

Free radical creation as a result of cigarette smoking may accelerate plaque and lesion formation due to endothelial injury from increased lipid peroxidation, suggesting this may be the mechanism responsible for the relationship between smoking and atherosclerosis [40]. Lipid peroxidation is responsible for the development of reactive oxygen species within the vasculature, and high levels of these oxygen species can cause a modification (oxidation) of the LDL particle [72].

Oxidized LDL can cross the protective barrier and lodge itself into the endothelial wall, which stimulates a natural immune defense with macrophages, leukocytes and monocytes. This immune defense will then release paracrine factors that attract platelets to the damaged endothelial site. These platelets aggregate and create foam cells, which is the first step in the development of the atherosclerotic plaque.

Research has shown that negative correlation also exists between smoking and clotting time as a result of enhanced platelet aggregation [73,74]. Furthermore, a smoker's ability to produce NO, a compound responsible for the smooth muscle dilation in the vasculature, is impaired [75,76]. The result is an inability to initiate vasodilation during times of hypoxia, further complicating the smoker's physiological adaptive responses.

Another indicator of coronary health is the size of the intima relative to the thickness of the cholesterol plaque. Cigarette smoking promotes stenosis and a reduced wall to plaque ratio, as well as extensive production of fatty streaks [77–79].

It is important to note that cigarette smoke contains over 4000 known components and only a select few have been studies in isolation [64]. It may be plausible to suggest that while each of these single components may exert minimal effects, in combination the evidence is overwhelming stating that cigarette smoke does contribute to cardiovascular disease through various mechanisms, such as exacerbations lipid profile. A more detailed description of the additional factors related to heart disease affected by smoke, e.g. vasomotor dysfunction, inflammation and thrombosis, can be found in a review by Ambrose and Barua [64].

9. Gender differences in cigarette smoking and CVD

It is important to briefly mention the sex differences that potentially exist between males and females with regards to smoking and the incidence of CVD. A recent study by Vidrine et al. [80] examined gender differences in adolescents on smoking outcomes and found that there were significant differences in smoking behavior. Specifically, boys smoked because of the buzz, pleasure, taste/smell or stimulation and did not smoke because of impairment of sport. Girls' major reasoning for smoking was weight control. For women this rationale persists following adolescence and maybe augmented by the increase in female hormones during puberty and years following [81]. This puts women at a particularly greater risk for development of CVD compared to men. Evidence suggests that for the same number of cigarettes smoked, women have twice the CVD risk compared to men [82]. This is perhaps due to the influence of hormones that have been cited to cause an increase in cravings, especially in the luteal phase [82]. Research also supports that both relative and absolute values of HDL cholesterol is reduced in women compared to men [12,111]. When stratified by serum HDL the incidence for myocardial infarction was higher in men than women in smokers compared to non-smokers. Furthermore, the PROCAM study [83] reported similar mean HDL and TG between men and women, however reported that the mean increase in TC for women was twice that of men and LDL cholesterol was four times greater. In addition, this led to a 1.5-fold increase in the LDL/HDL ratio in women compared to men [83]. The greater perturbations seen in the lipid/lipoprotein profile of smoking women could partially explain their greater risk for cardiovascular events compared to men.

10. Smoking cessation and nicotine replacement therapy

The World Health Organization's MONICA project reaffirmed in 2000 that cigarette smoking was one of the most powerful factors contributing to CVD [84], and smoking cessation is strongly recommended. Early studies [23,24] reported that those individuals who quit smoking had a substantial decrease in risk for acute myocardial infarction as compared to those who continued to smoke. Since 1970, several studies have affirmed that the decrease in incidence of CVD and acute myocardial infarction is greatest among those who stop smoking [114]. Moreover, it has been observed that smoking cessation can delay the onset of atherosclerosis by 10 years as compared to individuals who continue to smoke [85].

Research has shown a definite adaptation period after smoking cessation before risk of CVD is diminished, and

Table 1
Selected results from smoking cessation studies

Reference	Subjects	Interval period (days)	Intervention method	HDL-C (mmol)	TC	LDL-C	TG
Shennan et al.	21	365	None	↑ 0.18	NA	NA	↓ 0.23
Moffatt et al.	10	77	Nicotine patch	↑ 0.17	NA	NA	NA
Eliasson et al.	17	56	None	↑ 0.20	↓ 0.10	↓ 0.30	0.00
Moffatt	12	30	Cessation program	↑ 0.32	↓ 0.38	NA	↓ 0.06
Stamford et al.	13	48	Quit smoking kits	↑ 0.18	↑ 0.10	NA	↓ 0.20
Stubbe et al.	10	42	Group support	↑ 0.24	NA	NA	NA
Allen et al.	78	42	None	↑ 0.06	0.00	↓ 0.02	↑ 0.10
Quensel et al.	24	21	None	↑ 0.02	↑ 0.10	↑ 0.02	↑ 0.04
Moffatt et al.	7	30	Cessation program	NA	↑ 0.04	0.00	↓ 0.14
Gerace et al.	1233	2190	Special intervention	↑ 0.01	↓ 0.28	↓ 0.30	NA
Niaura et al.	9	84	Cessation program	↑ 0.13	↑ 0.05	↓ 0.10	↑ 0.07

this can take as little as 2 years to as many as 20 years [86]. Notwithstanding the need to traverse an adaptation period that may vary in length, smoking cessation ultimately bestows the reward of a reduced risk for CVD comparable to the level of those who have never smoked [87–90]. This should serve as a strong incentive to smokers to quite smoking.

Many physiologic benefits are associated with smoking cessation, including normalization of the lipid and lipoprotein profile. A meta-analysis by Maeda et al. [91] suggests that with smoking cessation an individual can experience an increase in HDL-C, but other lipid and lipoproteins (TC, LDL-C, TG) remain unchanged. Movement toward normalization of HDL-C can be seen in as little as 17 days [92] and will continue to progress toward normal (non-smoking) levels as long as cessation continues [92–96]. These results have important implications, because they will alter the ratios of HDL-C:TC and HDL-C:LDL-C and promote enhanced clearance of cholesterol from the circulation.

Nicotine is an addiction and smoking cessation is a challenge. Use of nicotine replacement therapy (NRT) in the form of chewing gum, patches and nasal spray can help manage cravings and reduce the hold of addiction. But, what are the physiologic effects of NRT? Early studies [97–99] indicated that administration of a nicotine patch does not alter lipids or lipoproteins, and one study [98] suggests that HDL-C can return to baseline on the patch.

However, more recent research does not support that original hypothesis [48]. Moffatt et al. [48] examined 10 male and 17 female smokers who refrained from smoking for 77 days. The subjects were asked to wear a nicotine patch for the first 35 days of their cessation and later asked to remove the patch and leave it off for the remainder of the cessation period (42 days). Subjects were analyzed in the postprandial state at 0 days (start of the study), 35 days (nicotine patch period) and 77 days (total smoking/nicotine abstinence for 42 days). HDL-C, HDL_2-C and HDL_3-C were reduced in smokers compared to non-smokers, and these differences were still present after the initial 35 days of cessation while on the nicotine patch. Within the following 42 days and without the influence of nicotine, lipoproteins normalized to those of non-smoking controls. This suggests that nicotine prevents normalization of HDL-C and its subfractions, but that effects are acute and persist only as long as the patch is in place. Thus, although NRT may impede normalization of blood lipids and lipoproteins, it is a more desirable alternative to smoking, as well as a helpful means to successful smoking cessation, assuming that use of NRT is temporary (summary of results in Table 1).

The gender difference exists also with smoking cessation showing that men are more likely to quit smoking, despite perhaps being heavier smokers. Research shows that although women report making attempts to change their behavior more frequently then men the success rate is less [100]. One factor again that seemed to contribute to this was overweight females were less likely to stop smoking than overweight males. Furthermore, when comparing males to females using NRT, Cepeda-Benito et al. [101] found that NRT was successful in females when giving in conjunction with high-intensity nonpharmacological support. Further, long term maintenance of NRT gains will decrease more rapidly for females, especially when support diminished. A review by Carpenter et al. [82] found that some of the 13 studies examined cited that nicotine dependence and withdrawal seemed to be mediated by hormonal fluxuations. Specifically, cravings and withdrawal symptoms were heightened during the luteal phase making it more difficult for women to stop smoking.

11. Metabolic changes after smoking cessation

The cessation of smoking will initially result in a metabolic withdrawal syndrome that affects 80% of all smokers [102,103]. Symptoms include restlessness, irritability, anxiety, and confusion. The impact of such symptoms are compounded by weight gain, an increase in waist to hip ratio, and an increased percent body fat due to increased caloric intake and/or decreased resting metabolic rate [48,57,94,104–106].

Does HDL-C normalization occur despite weight gain? The answer appears to be, yes, suggesting that smoking is a more potent mediator of alterations in the lipid and lipoprotein profile than weight gain. Stamford et al. [94] found that subjects increased their caloric intake by 227 kcal per day,

accounting for 69% of the significant weight gain following cessation. But, there was still a substantial proportion of the weight gain (31%) that could not be explained by increased kcal consumption, suggesting a significant decrease in resting metabolic rate (RMR) after smoking cessation, which was found to be the case [105]. A decrease in RMR can be explained by removal of stimulation of the nicotinic receptors and dampening the surge of catecholamine release.

Additional mechanisms that potentially contribute to weight gain have been investigated. Oeser et al. [106] examined circulating leptin levels and the lipid profile. Leptin is known to be a powerful regulator of appetite and is thought to be altered by smoking and/or cessation. Results showed that 7 days of nicotine abstinence produced no differences in fasting leptin levels or plasma concentrations of glucose, insulin or free fatty acids. Because nicotine abstinence was imposed for 7 days only, potential effects of circulating blood markers beyond 7 days is unknown.

A study by Niaura et al. [107] examined eighteen female smokers who quit smoking for 12 weeks. Subjects were divided into two groups ($n = 9$), the first group quit smoking using standard behavioral methods combined with exercise, and the second group used standard behavioral methods with no exercise intervention. Results of this study also found, similar to the above studies, that smoking cessation caused an increased total caloric intake, but in the control group only, not the exercise group. Furthermore, HDL-C significantly increased ($9.6\ \mathrm{mg\ dL^{-1}}$, $p < 0.01$) in the exercise group. There also was an increase in HDL-C in the control cessation group ($5.0\ \mathrm{mg\ dL^{-1}}$), but it did not reach statistical significance. These results suggest that exercise may override the increased caloric intake anticipated with cessation, and exercise may augment the positive changes seen in HDL-C.

12. Conclusions

Cigarette smoking is a major risk factor for CVD and exerts negative effects on the lipid and lipoprotein profile. Research indicates that at any given level of serum TC the relative risk for CVD and all-cause mortality is significantly higher in smokers, ranging from 1.57 to 2.78, and is evident even among those smokers who demonstrate a favorable TC concentration. Smoking decreases the cardio-protective HDL-C and may increase levels of TC, TG and LDL-C. Furthermore, cigarette smoking can alter the critical enzymes of lipid transport, lowering LCAT activity and altering CETP and HL activity. These factors would favor progression of atherosclerosis.

Smoking cessation will result in significant increases in HDL-C within 17 days and will continue to improve as cessation is sustained. Mixed results have been reported on the efficacy of nicotine replacement therapy (NRT), as some research suggests increased HDL-C concentrations, while others conclude there is no lipoprotein increase until NRT has been removed. Finally, weight gain is associated with smoking cessation, but HDL-C levels still increase toward normal despite this gain.

The ultimate conclusion is irrefutable. Considerable research evidence provides strong support for cessation from smoking as a means to alleviate excess risk for CVD and perturbations in lipid and lipoprotein profiles.

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