Effect of Smoking Cessation on Lipoprotein A-I and Lipoprotein A-I:A-II Levels

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Cigarette smoking is associated with low plasma high-density lipoprotein cholesterol (HDL-C) and apolipoprotein (apo) A-I levels, which may explain, in part, its deleterious effects on coronary heart disease (CHD). In a group of ex-smokers, we assessed the influence of smoking cessation on apo A-I particle levels. Plasma lipid, apolipoprotein, and lipoparticle concentrations of 58 subjects who had completely stopped smoking (ex-smokers) were compared with those of 37 subjects who had continued smoking (smokers) before and after a smoking cessation counseling program. Nutritional intake was recorded before and after the program to adjust for potential interaction with plasma lipid variables. Smokers and ex-smokers were similar in gender distribution, age, body mass index (BMI), social status, and nutrient intake. There were significantly greater increases in total cholesterol ($P < .04$), HDL-C ($P < .005$), HDL_2-C ($P < .008$), and lipoprotein (Lp) A-I:A-II ($P < .04$) in ex-smokers than in smokers. After smoking cessation, ex-smokers consumed more vegetable protein ($P < .02$) and polysaccharides ($P < .04$) and had higher plasma levels of HDL-C ($P < .0004$), apo A-I ($P < .001$), Lp A-I ($P < .007$), and Lp A-I:A-II ($P < .01$) than smokers. Adjustments on nutritional variables did not show any additional difference between ex-smokers and smokers, suggesting that smoking per se affects Lp A-I and Lp A-I:A-II levels. In conclusion, HDL particles including Lp A-I and Lp A-I:A-II are higher in ex-smokers than in smokers.
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CIGARETTE SMOKING is associated with coronary heart disease (CHD).[1-3] Several mechanisms may explain this association, including altered blood coagulation, impaired integrity of arterial walls, and changes in blood lipid, apolipoprotein, and lipoprotein levels. Several studies have demonstrated clear relationships between smoking and plasma lipoprotein levels, such as a dose-dependent decrease of high-density lipoprotein (HDL) levels.[4-14] Adolescents who become smokers show a greater decline in plasma HDL cholesterol (HDL-C) concentration than their nonsmoking peers.[4] Other studies have shown a rapid increase in HDL-C concentrations 2 to 6 weeks after smoking cessation.[14-17]

HDL particles are heterogeneous in size, hydrated density, and electrophoretic mobility.[18-19] Ultracentrifugation or precipitation methods identify two major different classes of HDL, HDL_2 and HDL_3. An additional classification based on apolipoprotein (apo) A-I content has been proposed. Accordingly, two major lipoparticle classes have been identified: one with apo A-I but no apo A-I (lipoprotein [Lp] A-I) and another with both apo A-I and apo A-II (Lp A-I:A-II).[20] Such a definition highlights the biochemical and functional differences between lipoproteins of similar hydrated density. As for HDL-C,[21,22] a decrease in plasma Lp A-I and Lp A-I:A-II is associated with a higher CHD risk.[23-25] Thus, to identify the origin of variability in the plasma Lp A-I level is of primary interest.

Accordingly, we investigated the influence of smoking cessation on plasma apo A-I–containing lipoproteins, taking into account the effect of environmental confounders such as body weight, nutritional intake, and alcohol consumption. Since the latter variables influence Lp A-I levels, on one hand, and are affected by smoking cessation, on the other hand, it was necessary to adjust for their potential confounding effects.

SUBJECTS AND METHODS

Population

Smokers participating in a smoking cessation counseling program were recruited in this study (N = 101). The program was based on five 1.5-hour daily sessions. Each subject was instructed with regard to the beneficial effect of smoking cessation and was provided psychological support to reduce the physical dependence of nicotine withdrawal. Each subject underwent two examinations, the first before the initial session and the second 3 to 12 weeks later. Subjects with triglycerides greater than 4.6 mmol/L (n = 4) or who smoked only cigars or a pipe (n = 2) were excluded. Participants were then classified into two groups: smokers that completely stopped tobacco consumption following the counseling program (ex-smokers, n = 58) and smokers that continued smoking (smokers, n = 37).

Data Collection

Smoking habits, medical history, socioeconomic status, and medication use, including oral contraceptives, were evaluated using a self-administered questionnaire validated by a physician in the presence of the subject. Smoking intoxication was estimated as the number of cigarettes smoked daily. Carbon monoxide was measured in the expired air to confirm self-reported smoking consumption data. Four social categories were defined according to the French National Statistical Institute for Economic Studies classification of occupational and social categories: 1, craft workers, shop owners, managers, senior executives, professors, and engineers; 2, middle-rank executives and technicians; 3, employees, personal service workers, military personnel, police, and skilled and unskilled workers. Housewives and inactive or unemployed people were included in a single category (group 4). Height and weight were measured, and body mass index (BMI) was calculated (kilograms per meter of height squared).

Each subject was interviewed by a registered dietician before and after the program. Food intake was evaluated by means of a 3-day food report in which participants were asked to indicate in detail their daily food and drink intake and the portion size in usual household measures

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during 2 randomly selected regular weekdays and 1 weekend day. They also had to explain their cooking methods and specify the type of fat used, including shortening and dressing. The questionnaire was reviewed and validated by a registered dietician. Quantities were translated into grams of food by the dietician before analyzing the questionnaire. A computerized dietary analysis system (NUTRI software[26]) was used to convert the collected data for nonalcoholic energy to kilojoules per day and nutrient intake and alcohol consumption to grams per day.[27]

Plasma Lipid, Lipoprotein, and Apolipoprotein Levels

Venous blood samples were drawn into EDTA tubes by venipuncture after an overnight fast. Plasma total cholesterol (assay variation: interassay, 1.3%; intraassay, 1.0%) and triglycerides (1.8% and 1.1%) were determined by enzymatic methods (Boehringer, Mannheim, Germany) adapted to a Hitachi 705 analyzer (Boehringer). An estimate of the low-density lipoprotein cholesterol (LDL-C) level (4.1% and 2.9%) was obtained with the Friedewald formula.[28] Cholesterol was determined in the HDL-containing supernatant after phosphotungstate/magnesium chloride precipitation (4.4% and 2.7%). HDL_2-C (5.0% and 3.0%) was quantified by subtracting HDL_3-C (5.0% and 3.0%), measured after polyethylene glycol precipitation, from HDL-C. Apo A-I (3.7% and 2.5%) and apo B (4.0% and 2.6%) were quantified by immunonephelometry (Behringwerke, Marburg, Germany). Lp A-I (4.5% and 2.6%) was determined by differential electroimmunoassay on ready-to-use plates (SEBIA, Issy les Moulineaux, France). Lp A-I:A-II (4.5% and 2.6%) was estimated by subtracting Lp A-I from apo A-I.

Statistical Analysis

Data were analyzed using the SAS statistical software release 6.10 (SAS Institute, Cary, NC). Logarithmic transformation was performed on triglyceride measurements for statistical analysis. Correlations between quantitative variables were tested with Pearson's correlation coefficients. Qualitative data were analyzed with χ^2 statistical tests using Yates correction when necessary. Carbon monoxide levels of smokers versus ex-smokers were tested using a nonparametric Wilcoxon's test. Changes between baseline and after intervention were calculated for each biological variable. Differences between the two groups (ex-smokers and smoker control group) were tested after adjustment using a general linear model.

RESULTS

Table 1 summarizes the clinical and economic characteristics and smoking habits of the subjects. The group of ex-smokers consisted of 58 subjects (20 women and 38 men) who reported complete cessation. The group of smokers included 37 subjects (15 women and 22 men) who failed to stop smoking. There were no statistically significant differences between smokers and ex-smokers with respect to gender distribution, age, body mass index (BMI), age of smoking onset, duration of tobacco intoxication, and percentage of individuals who inhaled smoke. There was a trend to a higher level of social status in the ex-smoker group, although not reaching the level of significance.

However, there were differences in the number of cigarettes smoked daily and the amount of carbon monoxide expired. Smokers smoked more cigarettes and expired more carbon monoxide than ex-smokers (Table 1). The smoking cessation program was associated with significant changes in smoking habits in both ex-smokers and smokers. By definition, ex-smokers decreased the number of cigarettes from 22.2 ± 9.5 to 0. This change was associated with a significant decrease in the amount of expired carbon monoxide between the two visits, from 23.3 ± 15.8 to 2.7 ± 1.9 ppm ($P < .0001$). Smokers reduced the number of cigarettes from 26.7 ± 11.0 to 16.2 ± 9.7 ppm ($P < .0001$). This change was associated with a significant decrease in the amount of expired carbon monoxide between the two visits, from 28.0 ± 13.8 to 16.8 ± 9.3 ppm ($P < .0003$). However, the amount of carbon monoxide expired was significantly higher in smokers than in ex-smokers after the program. There was no difference between the two groups in the interval between the initiation of the program and the second visit (ex-smokers, 5.0 ± 2.0 weeks; smokers, 5.5 ± 1.6 weeks). Thus, both ex-smokers and smokers were comparable at baseline for all variables except the number of cigarettes smoked daily and expired carbon monoxide levels.

Table 1. Clinical and Socioeconomic Characteristics and Smoking Habits According to Final Smoking Status of Subjects (mean ± SD)

Characteristic/ Habit	Smokers	Ex-smokers	*P*
No. of subjects	37	58	
Gender (women/men)	15/22	20/38	NS
Age (yr)	41.8 ± 11.1	39.6 ± 10.7	NS
BMI (kg/m²)	23.7 ± 3.0	23.7 ± 3.5	NS
Social category (%)			NS
1	13.5	35.0	
2	19.0	24.0	
3	40.5	24.0	
4	27.0	17.0	
Smoking habits			
Age of onset (yr)	18.0 ± 3.9	17.2 ± 3.6	NS
Duration of intoxication (yr)	14.2 ± 10.2	12.8 ± 9.5	NS
Smoke inhalation (%)	84	95	NS
Before the program			
No. of cigarettes/d	26.7 ± 11.0	22.2 ± 9.5	<.04
Carbon monoxide (ppm)	28.0 ± 13.8	23.3 ± 15.8	<.05
After the program			
No. of cigarettes/d	16.2 ± 9.7	0	
Carbon monoxide (ppm)	16.8 ± 9.3	2.7 ± 1.9	<.0001

Table 2 shows the energy and nutrient intake of smokers and ex-smokers before and after the smoking cessation program. There were no statistically significant differences in energy and nutrient intake at baseline and no detectable changes in food intake during the program between smokers and ex-smokers. After the smoking cessation program, there were few significant differences in nutrient intake: ex-smokers had a higher intake of vegetable proteins ($P < .02$) and polysaccharides ($P < .04$) than smokers. There were no other significant differences in nutrient and energy intake between the two groups.

Table 3 presents lipid values for smokers and ex-smokers. There were no statistically significant differences in plasma lipid, lipoprotein, apolipoprotein, and lipoparticle levels between the two groups at baseline. However, there was a significant correlation between the number of cigarettes smoked daily and plasma levels of triglyceride ($r = .22$, $P < .04$), HDL_3-C ($r = -.21$, $P < .04$), and Lp A-I ($r = -.22$, $P < .03$), but not Lp A-I:A-II ($r = +.06$, NS). After the intervention,

Table 2. Daily Energy and Nutrient Intake (mean ± SD) Before and After the Smoking Cessation Program According to Final Smoking Status of Subjects

Intake	Before Program			After Program		
	Smokers (n = 37)	Ex-smokers (n = 58)	P*	Smokers (n = 37)	Ex-smokers (n = 55)‡	P†
Nonalcoholic (kJ/d)	9,163 ± 2,718	9,001 ± 2,373	NS	8,715 ± 3,353	9,533 ± 3,193	NS
Total protein (g/d)	87 ± 23	84 ± 22	NS	82 ± 28	90 ± 30	NS
Animal (g/d)	65 ± 19	60 ± 20	NS	61 ± 21	65 ± 23	NS
Vegetable (g/d)	22 ± 8	24 ± 8	NS	21 ± 8	25 ± 12	<.02
Total fat (g/d)	105 ± 35	102 ± 35	NS	102 ± 41	109 ± 45	NS
Animal (g/d)	76 ± 25	71 ± 29	NS	73 ± 30	76 ± 35	NS
Vegetable (g/d)	29 ± 18	31 ± 17	NS	29 ± 18	33 ± 19	NS
Polyunsaturated (g/d)	16 ± 11	14 ± 9	NS	14 ± 9	15 ± 10	NS
Monounsaturated (g/d)	33 ± 11	33 ± 12	NS	34 ± 16	36 ± 14	NS
Saturated (g/d)	44 ± 14	42 ± 16	NS	42 ± 16	45 ± 23	NS
P/S ratio	0.36 ± 0.18	0.36 ± 0.20	NS	0.33 ± 0.11	0.35 ± 0.18	NS
Cholesterol (mg/d)	470 ± 189	461 ± 230	NS	476 ± 234	490 ± 239	NS
Total carbohydrate (g/d)	223 ± 86	224 ± 69	NS	208 ± 92	232 ± 87	NS
Oligosaccharides (g/d)	107 ± 61	93 ± 43	NS	95 ± 58	98 ± 48	NS
Polysaccharides (g/d)	116 ± 44	131 ± 45	NS	113 ± 53	134 ± 63	<.04
Alcohol (g/d)	28 ± 28	25 ± 21	NS	31 ± 32	27 ± 21	NS

Abbreviations: NS, not significant; P/S ratio, polyunsaturated to saturated ratio.

*Adjusted for gender, age, BMI 1, socioeconomic status, and cigarettes 1.

†Adjusted for gender, age, BMI 2, socioeconomic status, cigarettes 1, and the interval between the examinations.

‡Three subjects have not completed the second dietary record.

multivariate analysis adjusting for gender, age, BMI, socioeconomic status, number of cigarettes smoked daily, and the interval between the examinations demonstrated significant differences in lipid variables between the two groups. At the second visit, plasma HDL-C ($P < .0004$), HDL_2-C ($P < .0007$), HDL_3-C ($P < .001$), apo A-I ($P < .001$), Lp A-I ($P < .007$), and Lp A-I:A-II ($P < .01$) concentrations were higher in ex-smokers than in smokers. Since alcohol consumption is an important determinant of plasma HDL and apo A-I levels, the data were adjusted for alcohol consumption. This adjustment did not change the results of analyses comparing ex-smoker and smoker groups. Further adjustment for other nutritional variables (nonalcoholic energy, vegetable protein, and polysaccharide intakes) showed no additional significant differences between the two groups in lipid, lipoprotein, and apolipoprotein levels.

Table 4 presents changes in body weight and biochemical variables for the smokers and ex-smokers. The program was associated with a significantly larger increase in body weight ($+2.4 \pm 2.5$ *v* $+0.7 \pm 1.9$ kg, $P < .002$) and BMI ($+0.8 \pm 0.8$ *v* $+0.3 \pm 0.6$ kg/m^2, $P < .002$) in ex-smokers than in smokers. However, these changes failed to result in a statistically significant difference in body weight (70.0 ± 13.7 *v* 72.5 ± 13.6 kg) or BMI (23.9 ± 3.0 *v* 24.3 ± 3.7 kg/m^2) between smokers and ex-smokers after the smoking cessation program. There were also statistically significantly greater increases in total cholesterol ($P < .04$), HDL-C ($P < .005$), HDL_2-C ($P < .008$), and Lp A-I:A-II ($P < .04$) in ex-smokers than in smokers. Thus, there is an apparent discrepancy in the results when the data are analyzed with values obtained after the smoking cessation program or with changes within the groups. This discrepancy is dependent on the heterogeneity of the variables and on the correlation between values obtained before and after the smoking cessation program. Accordingly, the present study

Table 3. Plasma Lipid, Apolipoprotein, and Lipoprotein Levels (mean ± SD) Before and After the Smoking Cessation Program According to Final Smoking Status of Subjects

Parameter	Before Program			After Program		
	Smokers	Ex-smokers	P*	Smokers	Ex-smokers	P†
No. of subjects	37	58		37	58	
Total cholesterol (mmol/L)	5.50 ± 1.20	5.38 ± 1.17	NS	5.34 ± 1.28	5.51 ± 1.05	NS
HDL-C (mmol/L)	1.33 ± 0.30	1.37 ± 0.36	NS	1.26 ± 0.25	1.50 ± 0.45	<.0004
LDL-C (mmol/L)	3.52 ± 1.04	3.38 ± 1.00	NS	3.41 ± 1.18	3.35 ± 0.93	NS
Triglycerides (mmol/L)	1.41 ± 0.60	1.37 ± 0.73	NS	1.43 ± 0.89	1.46 ± 0.85	NS
HDL_2-C (mmol/L)	0.19 ± 0.12	0.21 ± 0.12	NS	0.15 ± 0.08	0.27 ± 0.13	<.0007
HDL_3-C (mmol/L)	1.09 ± 0.29	1.17 ± 0.32	NS	1.07 ± 0.31	1.28 ± 0.35	<.001
Apo A-I (g/L)	1.48 ± 0.26	1.46 ± 0.26	NS	1.46 ± 0.23	1.56 ± 0.26	<.001
Apo B (g/L)	1.17 ± 0.34	1.12 ± 0.32	NS	1.13 ± 0.38	1.12 ± 0.29	NS
Lp A-I (g/L)	0.45 ± 0.12	0.48 ± 0.14	NS	0.46 ± 0.11	0.51 ± 0.16	<.007
Lp A-I:A-II (g/L)	1.03 ± 0.22	0.98 ± 0.18	NS	1.00 ± 0.17	1.06 ± 0.20	<.01

*Adjusted for gender, age, BMI 1, socioeconomic status, and cigarettes 1.

†Adjusted for gender, age, BMI 2, socioeconomic status, cigarettes 1, and the interval between the examinations.

Table 4. Change in Weight, BMI, and Plasma Lipid, Apolipoprotein, and Lipoprotein Levels (mean ± SD) According to Final Smoking Status of Subjects

Parameter	Smokers	Ex-smokers	P
No. of subjects	37	58	
Weight (kg)	+0.7 ± 1.9	+2.4 ± 2.5	<.002*
BMI (kg/m²)	+0.3 ± 0.6	+0.8 ± 0.8	<.002*
Total cholesterol (mmol/L)	−0.16 ± 0.56	+0.13 ± 0.73	<.04†
HDL-C (mmol/L)	−0.07 ± 0.20	+0.13 ± 0.26	<.005†
LDL-C (mmol/L)	−0.11 ± 0.52	−0.03 ± 0.65	NS†
Triglycerides (mmol/L)	+0.02 ± 0.65	+0.08 ± 0.76	NS†
HDL_2-C (mmol/L)	−0.04 ± 0.14	+0.06 ± 0.14	<.008†
HDL_3-C (mmol/L)	−0.02 ± 0.37	+0.11 ± 0.21	NS†
Apo A-I (g/L)	−0.02 ± 0.15	+0.10 ± 0.21	<.01†
Apo B (g/L)	−0.04 ± 0.18	+0.00 ± 0.17	NS†
Lp A-I (g/L)	+0.01 ± 0.11	+0.03 ± 0.10	NS†
Lp A-I:A-II (g/L)	−0.03 ± 0.17	+0.08 ± 0.19	<.04†

*Adjusted for gender, age, socioeconomic status, alcohol change, cigarette 1, and the interval between the examinations.

†Adjusted for gender, age, BMI change, socioeconomic status, alcohol change, nonalcoholic energy change, cigarette 1, and the interval between the examinations.

could lack sufficient statistical power when the variability of the measurements is elevated or when the correlation between measurements is low.

DISCUSSION

The aim of the study was to investigate the influence of smoking cessation on plasma levels of apo A-I lipoprotein particles. The principal finding is that smoking cessation results in higher levels of HDL, HDL_2, HDL_3, apo A-I, Lp A-I, and Lp A-I:A-II.

Only a few studies have analyzed the effects of smoking cessation on lipid parameters.[14-17,29] Most of these investigations showed an increase of HDL-C in ex-smokers. However, the conclusions of these reports are limited by the small number of subjects,[14,16,29] lack of a control group,[16,29] or missing dietary records.[15] The present study indicates that HDL concentration is affected by short-term smoking cessation independently of food and alcohol intake. HDL-C, HDL_2-C, apo A-I, and Lp A-I:A-II increased after smokers stopped tobacco intoxication. A dose-response association has been described for HDL-C[5,8] and apo A-I,[5,8,30] but was never demonstrated for Lp A-I:A-II. This relationship can be attributed to the influence of smoke components on enzymes that regulate lipoprotein metabolism such as lecithin:cholesterol acyltransferase[5,31,32] or hepatic lipase.[31] Thus, a reduction in the number of cigarettes smoked daily is associated with beneficial changes in the lipoprotein profile.

Several limitations must be taken into account in interpretation of the results. Firstly, changes in lipid levels were examined only a few weeks after initiation of the program, thereby limiting our conclusions to short-term duration. However, several transversal studies have reported no differences in HDL-C between never-smokers and smokers who had stopped smoking for longer than 1 year,[6,7] suggesting that the increase in HDL-C levels persists for a long time. Secondly, as in other studies,[33-34] the controls (ie, smokers) smoked more cigarettes than the ex-smokers did before. This observation results directly from the design of the study. The control group was selected from among smokers who were involved in the same smoking cessation program but did not succeed in quitting. This strategy was necessary to improve the comparability of ex-smoker and control groups. Therefore, the analyses were adjusted on the baseline daily cigarette consumption to account for this difference. Thirdly, another potential confounding factor consists of the association of smoking cessation and changes in nutritional habits. The latter changes may explain part of the lipid, apolipoprotein, or lipoprotein variations in ex-smokers.[16,35] The biological data were systematically adjusted for nutritional variables to control this effect. Fourthly, some smokers in the control group decreased cigarette consumption after the program. Such an action, if it affects plasma lipoprotein levels, would decrease the expected contrast between the two groups and thus the power of the study.

Several studies have shown anthropometric and nutritional changes in smokers who stop smoking.[16,35,36] Since both tobacco intoxication and nutritional variables affect lipid and lipoprotein levels, this factor may potentially interact to regulate lipoprotein levels. In the present study, smokers gained weight significantly when they stopped smoking. This is usually associated with a decrease in HDL and apo A-I levels.[37-38] Thus, the finding of an increase in apo A-I–containing particles despite the weight gain suggests that the effect of smoking cessation overcomes the effect of weight change. Several changes in nutritional variables were observed after smoking cessation.[14,16,17,35] They may either aggravate or attenuate changes in the lipid profile. Therefore, the observation of changes in lipoprotein levels independently of nutritional modification, including alcohol consumption, further suggests that smoking per se has an effect on apo A-I–containing lipoproteins.

In agreement with several studies,[14-17] there were no detectable changes in total cholesterol and triglyceride levels after smoking cessation. Several hypotheses may account for this observation: (1) the study was too short to allow for significant changes in apo B–containing lipoprotein levels to occur; (2) the higher variability of cholesterol and triglyceride levels compared with HDL-C levels decreases the statistical power of the analyses; (3) the effects of nutritional factors on these parameters may confound their potential changes; and (4) the tobacco component may not affect apo B–containing lipoprotein metabolism.

In conclusion, we demonstrated that smoking cessation is associated with higher levels of HDL, HDL_2, HDL_3, apo A-I, Lp A-I, and Lp A-I:A-II. Because of their role in reverse cholesterol transport, apo A-I–containing particles represent an antiatherogenic lipoprotein fraction. The increase in the latter lipoparticles after cessation of cigarette smoking may contribute to the decrease of CHD risk in ex-smokers.[3,39]

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