Clin. Cardiol. 25, 23–26 (2002)

Smoking Cessation, but Not Smoking Reduction, Reduces Plasma Homocysteine Levels

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Summary

Background: Cigarette smoking has been associated with increased plasma homocysteine levels. Although hyperhomocysteinemia may mediate some of the adverse cardiovascular consequences of smoking cigarettes, the effects of smoking cessation and smoking reduction on homocysteine levels have not been evaluated previously.

Hypothesis: The purpose of this study was to determine the effects of smoking cessation and smoking reduction on plasma homocysteine levels.

Methods: Fifty-one healthy subjects who smoked 35.9 ± 6.4 cigarettes daily were randomized to continue smoking, reduce smoking to 4–8 cigarettes daily, or to stop smoking. A nicotine inhaler and individualized counseling were provided as aids to smoking cessation.

Results: In subjects who quit smoking, homocysteine levels decreased by 11.6%, from 8.58 ± 2.31 to 7.53 ± 2.26 µmol/l ($p = 0.013$). Significant changes in homocysteine levels were not observed in subjects who reduced smoking or continued to smoke.

Conclusion: A "harm reduction" strategy of reducing cigarette use may not be sufficient for reducing the vascular risk associated with smoking cigarettes.

Key words: homocysteine, tobacco, atherosclerosis

Introduction

Tobacco abuse and elevated total plasma homocysteine (Hcy) levels are independent and additive risk factors for atherosclerotic vascular disease.[1–7] Cigarette smoking, the leading avoidable cause of death and morbidity in the United States, has been associated with increased Hcy levels.[1–5, 8] In the Hordaland Homocysteine Study, smoking ≥ 20 cigarettes daily was associated with a 2.01 µmol/l increase in Hcy levels, a finding that may be related to enhanced catabolism of vitamin B_6 and folate.[1, 4, 9–11] Although hyperhomocysteinemia may mediate some of the adverse cardiovascular consequences of smoking cigarettes, the effect of smoking cessation on Hcy levels has not been evaluated previously. Helping patients stop smoking remains a clinical challenge, however, and several barriers interfere with the ability of physicians to evaluate and treat smokers.[8] Because only 50% of smokers eventually quit smoking, a "harm reduction" strategy of reducing cardiovascular risk among ongoing smokers has been proposed recently.[12] It is not known, however, whether reducing cigarette use, rather than quitting, reduces Hcy levels. The purpose of this study was to determine the effects of smoking cessation and smoking reduction on Hcy levels.

Methods

Subjects were randomized to continue smoking at their current rate, reduce smoking to 4 to 8 cigarettes per day, or to stop smoking completely. A nicotine inhaler (Nicotrol® Inhaler, McNeil Consumer Products Company, Fort Washington, Pa.,

This study was funded by McNeil Consumer Products Company, Fort Washington, Pa.

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Received: December 7, 2000
Accepted with revision: April 27, 2001

TABLE I Vitamin levels at baseline and after 12 weeks

	Vitamin B_6 (ng/ml)		Vitamin B_{12} (ng/ml)		Folate (ng/ml)	
	Baseline	Week 12	Baseline	Week 12	Baseline	Week 12
Continue	13.1 ± 8.5	15.8 ± 11.9	441 ± 210	439 ± 153	9.5 ± 4.5	9.1 ± 2.9
p Value	0.405		0.898		0.746	
Reduce	15.8 ± 19.2	11.4 ± 10.4	290 ± 130	333 ± 177	8.7 ± 2.6	10.5 ± 4.3
p Value	0.147		0.236		0.241	
Quit	18.2 ± 12.8	15.5 ± 9.7	344 ± 158	348 ± 154	12.8 ± 4.7	12.2 ± 12.2
p Value	0.618		0.883		0.693	

Continue = continued smoking; Reduce = reduced smoking; Quit = stopped smoking.
All values are mean ± standard deviations of the mean.

USA) and individualized counseling were provided as aids to smoking cessation and reduction. Subjects were considered to have quit smoking if they reported no cigarette use for 1 week and had an exhaled carbon monoxide level < 10 ppm (Quit group). They were considered to have reduced smoking if they reported a ≥ 50% reduction in cigarette use but did not quit (Reduce group). The remaining subjects continued to smoke without changing their daily cigarette use (Continue group).

To be included in the study, subjects had to be medically healthy, smoke 30 to 60 cigarettes daily, have an exhaled carbon monoxide level > 9 ppm (Bedfont Scientific Ltd, Upchuron, Kent, UK). Subjects were excluded if they used non-cigarette tobacco products or had intensive exposure to second-hand smoke. Daily intakes of folic acid and B vitamins were assessed using a dietary inventory specially created for this study. Laboratory evaluations were performed in the fasting state at baseline and after 12 weeks. In our laboratory, the coefficient of variation for plasma Hcy levels is 3.6%, based on a test sample of 114 healthy volunteers with a mean (± standard deviation [SD]) plasma Hcy level of 9. 6 ± 0.33 µmol/l.

Continuous variables were described as means and SDs of the mean. Comparisons of changes in homocysteine values within groups were described by paired Student's *t*-tests corrected for multiple comparisons. Between-group changes were described by analysis of variance for baseline values. Analysis of covariance controlling for baseline homocysteine levels was used to compare 12-week values.

Results

Fifty-one smokers (23 men, 28 women, mean age 43.5 ± 10.3 years) were randomized. At baseline, subjects smoked 35.9 ± 6.4 cigarettes per day. In the Quit group, average cigarette use decreased from 35.0 to 0.0/day ($p < 0.001$). In the Reduce group, average cigarette use decreased from 35.9 to 9.0/day ($p < 0.001$). In the Continue group, cigarette use did not change significantly (37.6–36.0/day, $p = 0.433$). There were no differences between groups in baseline Hcy levels (8.9 ± 2.0 µmol/l).

Thirty-eight subjects completed the study; 13 subjects dropped out because of an inability to comply with the protocol. Data from five subjects were excluded prospectively because of severe hyperhomocysteinemia (> 16 µmol/l, n = 4) or failure to complete the dietary questionnaire (n = 1). These subjects were equally distributed among the three groups (two Quit, two Continue, one Reduce). Eight subjects successfully quit smoking, 15 reduced cigarette use, and 10 continued smoking cigarettes. Significant changes in serum levels of vitamin B_6, vitamin B_{12}, and folic acid were not observed among or within groups after 12 weeks (Table I). Although 12 subjects used multivitamins or B vitamin supplements, vitamin use was equally distributed among the three groups and did not change during the study ($p = 0.174$). Significant changes in dietary inventory scores, weight, serum cotinine, and serum nicotine levels also were not observed among or within groups (data not shown). Subjects in the Quit group used 48.6 ± 39.8 inhaler cartridges during the final 14 days of the study (approximately 3.5 cartridges/day). In the Quit group, Hcy levels decreased by 11.6%, from 8.58 ± 2.31 to 7.53 ± 2.26 µmol/l ($p = 0.013$, Table II, Fig. 1). Changes in Hcy levels in the Continue and Reduce groups were small and not statistically significant (Table II, Fig. 1). Differences among groups were not significant at baseline ($p = 0.254$) or after 12 weeks ($p = 0.149$).

Discussion

In this study, smoking cessation with the assistance of a nicotine inhaler and counseling significantly reduced Hcy levels, but a "harm reduction" strategy of reducing cigarette use did not.[12] Because dietary intake and serum levels of vitamins

TABLE II Homocysteine levels at baseline and after 12 weeks

	Number	Baseline	12 Weeks	Mean change	p Value
Continue [a]	10	9.13 ± 1.67	8.52 ± 1.11	−0.61 ± 0.54	0.124
Reduce [a]	15	9.03 ± 2.09	8.81 ± 1.96	−0.22 ± 0.12	0.411
Quit [a]	8	8.58 ± 2.31	7.53 ± 2.26	−1.05 ± 0.04	0.013

[a] See Table I footnotes.
All values are mean ± standard deviations of the mean in µmol/l

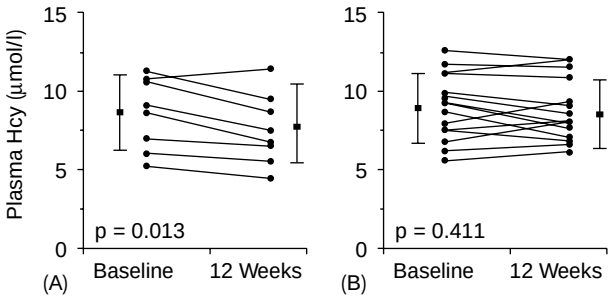

FIG. 1 Homocysteine levels at baseline and after 12 weeks. (A) Subjects who quit smoking cigarettes, (B) subjects who reduced cigarette use.

known to affect Hcy did not change, it is likely that the Hcy reduction in the Quit group was related to smoking cessation, not dietary changes. These changes also were observed despite the use of nicotine replacement therapy, which theoretically could raise Hcy levels.[13]

Recently, hyperhomocysteinemia has emerged as an independent risk factor for atherosclerosis in the coronary, carotid, and peripheral arterial beds.[1, 2, 6, 7] The adverse effects of smoking cigarettes on atherosclerotic vascular disease is well known; however, the pathophysiology underlying the relationship between cigarette smoking and atherosclerosis is complex and multifactorial.[8] One of the many adverse effects of smoking is increasing Hcy levels, which may contribute to endothelial injury and atherosclerosis.[1–5] It can reasonably be inferred, therefore, that smoking cessation should lead to a decrease in Hcy levels. To our knowledge, this is the first study that evaluated and verified this assumption.

More serious, however, is the observation that the vast majority of smokers do not intend to quit smoking in the next 6 months, and that only half of smokers eventually are successful at quitting.[12, 14] The recently proposed "harm reduction" strategy of decreasing cardiovascular risk by merely reducing the number of cigarettes smoked has not been tested.[12] In this study, although the "harm reduction" strategy led to decreased cigarette use, Hcy levels, one potential source of harm from cigarette smoking, did not decrease.

Although this study was small and of short duration, smoking cessation led to a significant reduction in Hcy levels, despite the fact that the subjects had normal or only mildly elevated Hcy levels. The relatively high drop-out rate observed in this study is typical of smoking cessation studies.[15, 16] Whether subjects with higher baseline Hcy levels would have had a more dramatic reduction in Hcy levels, or whether the observed Hcy reduction will persist with time, is not known.

The absolute reduction in homocysteine levels observed in this study was small; however, small changes in very prevalent risk factors can have striking effects on disease incidence in large populations. Indeed, the relative risk for the difference between Hcy levels of 10 and 15 µmol/l is 1.4, similar to the risk reduction expected by decreasing total serum cholesterol levels from 7.1 to 4.9 µmol/l.[2, 17] By extrapolation, if smoking cessation resulted in a 1 µmol/l reduction in Hcy levels, the relative reduction in risk of coronary events due to Hcy reduction may be as high as 17%.[17, 18] Of course, the atherosclerotic risk associated with cigarette smoking is related to many factors other than homocysteine elevation, such as hypercoagulability, myocardial work, coronary vasomotor tone, dyslipidemia, and oxidative stress which also would be expected to improve with smoking cessation.[13]

Although cigarette smoking has been associated with decreased levels of vitamin B_6, vitamin B_{12}, and folate—which may explain the direct relationship between smoking and homocysteine levels—changes in serum levels of these vitamins were not observed.[4, 9–11] Because of the small sample size, small changes in folate and B vitamin levels may not have been detected. Other mechanisms of smoking-induced hyperhomocysteinemia, such as endothelial injury, platelet activation, or chronic inflammation, also may have contributed to our findings. Finally, it is also possible that nicotine replacement therapy may have a direct homocysteine-lowering effect; however, this has not been tested.

Conclusion

In young to middle-aged smokers with normal to mildly elevated Hcy levels, smoking cessation, but not smoking reduction, reduced homocysteine levels. These findings suggest that a "harm reduction" strategy of merely reducing cigarette use may not be sufficient for reducing the vascular risk associated with smoking cigarettes.

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