

The Effects of Cigarette Smoking on Glycosylated Hemoglobin in Nondiabetic Individuals

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Cigarette smoking has been causally linked to atherosclerotic heart disease. The mechanism by which cigarette smoking causes heart disease has not, however, been determined. Nicotine has been shown to lead to increases in plasma epinephrine and norepinephrine following smoking. Catecholamines have been shown to lead to increases in blood glucose.

This paper demonstrates that cigarette smoking is associated with increases in average blood glucose as measured by glycosylated hemoglobin levels in smokers compared with nonsmokers. Fifteen nondiabetic smokers had an average glycosylated hemoglobin of 6.82% (SD = 1.06%), which is higher than the 5.63% (SD = .49%, $t = 3.98$, $P < .001$) found for 23 nonsmokers. The average glycosylated hemoglobin level of the smokers is in the range found for patients with well-controlled diabetes. These data suggest that elevated blood glucose may contribute to atherogenesis in cigarette smokers.

Cigarette smoking has been shown to cause atherosclerotic heart disease in smokers.¹⁻³ The Surgeon General's report² has presented convincing evidence that smokers have a greater incidence of atherosclerotic heart disease than nonsmokers, whereas patients who have smoked but give up the habit have a decreasing rate of heart disease, thus indicating a direct causal relationship between cigarette smoking and atherosclerosis. The mechanism by which cigarette smoking causes atherosclerosis remains obscure, however.

Nicotine has been demonstrated to increase plasma levels of norepinephrine and epinephrine.^{1,4-8} This increase in catecholamines is followed by an increase in heart rate and blood pressure as well as other changes attributed to increased adrenergic activity following cigarette smoking. None of these changes, however, can be directly linked to atherosclerosis in humans. Increases in plasma catecholamines have been known to cause increased hepatic glycolysis and gluconeogenesis and decreased pancreatic insulin secretion in humans,⁹⁻¹¹ leading to increased plasma glucose. One would expect, then, that cigarette smoking would lead to increased plasma glucose levels, especially when nicotine levels are high.

The literature on the effects of cigarette smoking on blood glucose is inconclusive. Sandberg et al¹² reported a transient increase of blood glucose levels from 4.21 mmol/L (75.8 mg/dL) to 4.93 mmol/L (88.8 mg/dL) within 30 minutes of smoking a cigarette. Similar results were reported by Bornemisza and Suci,¹³ by Murchison and Fyfe,¹⁴ and by Haggard and Greenberg.¹⁵ On the other hand, Cryer et al,⁸ Rehder and Roth,¹⁶ and Walsh et al¹⁷ found no effect of smoking on blood glucose levels.

The effects of cigarette smoking on average blood glucose levels as measured by glycosylated hemoglobin have as yet received little attention. This study was done to assess the effects of smoking on plasma glucose by comparing the glycosylated hemoglobin levels of subjects who smoked one pack per day or more with those of nonsmokers.

METHODS

This study was part of a larger study of the relationship of glycosylated hemoglobin to risk factors for atherosclerotic heart disease. Subjects were recruited for cholesterol screening, and were generally unaware of the hypotheses of this aspect of the study. Subjects were healthy, nondiabetic individuals (fasting blood glucose below 6.0 mmol/L, 108 mg/dL) who were on no medications known to affect blood glucose levels. Subjects ranged in age from 20 to 76 years,

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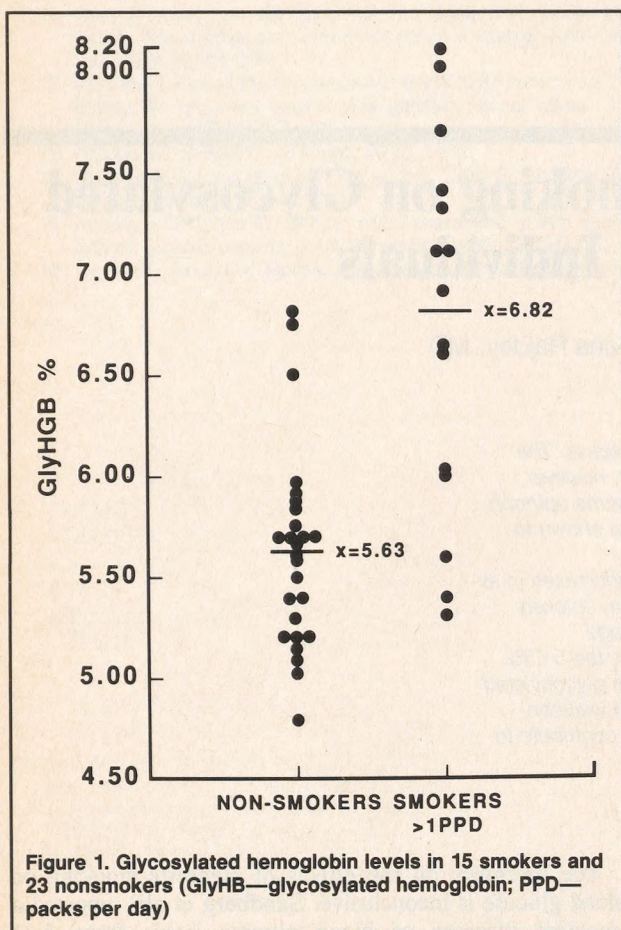


Figure 1. Glycosylated hemoglobin levels in 15 smokers and 23 nonsmokers (GlyHB—glycosylated hemoglobin; PPD—packs per day)

and represented thin and obese individuals in both the smoking and nonsmoking groups. They were recruited from the patient population of the local family practice center as well as from the professional staffs of the center and the local hospital. Smokers who averaged less than one pack per day were eliminated from the study. Nicotine content of cigarettes varies widely, and smokers differ widely in their smoking technique, making quantitation of the nicotine dose absorbed by an individual smoker from an individual cigarette difficult to estimate. No attempt was made to quantitate the level of smoking beyond the requirement of one pack per day or more. Fifteen smokers and 26 nonsmokers agreed to take part in the study. The average fasting blood glucose level of the smokers was slightly but not significantly lower than that of the nonsmokers, 4.14 mmol/L, SD = 1.12 mmol/L, (74.5 mg/dL, SD = 20.1 mg/dL) vs 4.47 mmol/L, SD = .52 mmol/L, (80.5 mg/dL, SD = 9.3 mg.dL, $t = 1.08$, not significant).

Blood was drawn from each subject after an overnight fast, and was analyzed for glucose and glycosylated hemoglobin. Glucose was measured by the standard glucose oxidase method. Glycosylated hemoglobin was measured by the boronate gel affinity chromatography method using the Endocrine Science kit.^{18,19} This method has been shown

to measure only the stable glycosylation product of hemoglobin; it is insensitive to the unstable Schiff base adduct, and thus is not affected by short-term changes in blood glucose. Glycosylated hemoglobin measured by this method has been shown to be a linear measure of average blood glucose over a wide range of values, with average glucose (mmol/L) = $.886 \times$ glycosylated hemoglobin + $.30$.¹⁸ This measure is more specific for average blood glucose than is the older hemoglobin A_{1c} determination.

Data analysis was done using Student's t test.

RESULTS

The 15 smoking subjects had glycosylated hemoglobin levels ranging from 5.30% to 8.14% with an average of 6.82% (SD = 1.06%). The 26 nonsmoking subjects had glycosylated hemoglobin levels ranging from 4.80% to 6.8% with an average of 5.63% (SD = 0.49%). These averages are significantly different ($t = 3.98$, $P < .001$). These results indicate that the smokers have an average blood glucose that is 20% higher than that of the nonsmokers. The data are displayed in Figure 1.

DISCUSSION

These results demonstrate a substantial and significant difference in average blood glucose levels between smokers and nonsmokers. The difference cannot be attributed to age differences. Normal subjects older than 60 years were reported to have an average glycosylated hemoglobin level of 5.7% (SD = 0.6%), which is only slightly higher than the 5.5% (SD = 0.5%) found for subjects younger than 60 years old.¹⁸ Obesity is well known to impair glucose tolerance, and obese subjects were found in the smoking and the nonsmoking group. The highest glycosylated hemoglobin levels in the smoking group were found in subjects who were not clinically obese, however, so obesity is unlikely to explain the differences found in glycosylated hemoglobin levels. The differences in glycosylated hemoglobin levels are probably not due to an increased frequency of borderline diabetes in the smoking group, as the smokers had, if anything, slightly lower fasting glucose levels than the nonsmokers.

Of the 15 smokers, 10 had glycosylated hemoglobin levels above 6.5%. This figure is in the range reported by the Endocrine Science group for patients with type II diabetes,¹⁸ suggesting that these subjects have average plasma glucose levels that are high enough to place them at risk for the same complications as those with well-controlled diabetes, including atherosclerotic heart disease.

The data reported here are consistent with the report of Sheridan-Pereira et al,²⁰ who found increased hemoglobin A_{1c} levels in pregnant smokers compared with those of nonsmokers. The present results are consistent also with the studies that found cigarette smoking to cause transient

increases in blood glucose,¹²⁻¹⁵ but do not support the negative results found by other authors.^{8,16,17}

It is clear from the Framingham study³ and many other studies that persons with diabetes have an increased risk of atherosclerotic heart disease compared with those who do not have diabetes. Since the majority of the smokers in this study had glycosylated hemoglobin levels in the diabetic range, the results presented here suggest that the elevations in average blood glucose in smokers compared with that in nonsmokers are adequate to explain some of the atherosclerotic heart disease known to be caused by cigarette smoking. Further study is needed to determine the clinical significance of this finding.

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