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ScienceDirect
Metabolism Clinical and Experimental 57 (2008) 1108–1114
Metabolism
Clinical and Experimental
www.metabolismjournal.com

Pioglitazone administration decreases cardiovascular disease risk factors in insulin-resistant smokers

Fahim Abbasi*, Helke M.F. Farin, Cindy Lamendola, Leigh McGraw, Tracey McLaughlin, Gerald M. Reaven

Stanford University School of Medicine, CA 94305, USA

Received 20 October 2007; accepted 17 March 2008

Abstract

Insulin sensitivity varies in cigarette smokers, and there is evidence that cardiovascular disease (CVD) risk is greatest in those smokers who are also insulin resistant. To extend these observations, we sought to (1) compare CVD risk factors in smokers who do not plan to stop smoking, divided into insulin-resistant (IR) and insulin-sensitive (IS) subgroups, and (2) evaluate the ability of drug-induced changes in insulin sensitivity to decrease CVD risk. Thirty-six cigarette smokers were divided into IR (n = 19) and IS (n = 17) subgroups by determining their steady-state plasma glucose (SSPG) concentrations during the insulin suppression test (the higher the SSPG, the more insulin resistant the individual). In addition, baseline measurements were made of fasting lipid and lipoprotein concentrations; inflammatory markers; and daylong glucose, insulin, and free fatty acid responses to test meals. All subjects were treated with pioglitazone for 12 weeks, after which all baseline measurements were repeated. Baseline triglyceride and high-density lipoprotein cholesterol concentrations were significantly different in IR as compared with IS smokers ($P < .05$) both before and after adjustment for differences in sex and body mass index. After pioglitazone treatment, SSPG concentration significantly fell in the IR smokers ($P < .001$), associated with a significant improvement in the atherogenic lipoprotein profile seen at baseline ($P \leq .03$) and a decrease in soluble intercellular adhesion molecule 1 and C-reactive protein concentrations ($P = .01$ and .02, respectively), whereas the IS smokers only had a significant increase in high-density lipoprotein cholesterol ($P = .004$) and a decrease in soluble intercellular adhesion molecule 1 ($P = .02$) and CRP ($P = .07$) levels. In conclusion, cigarette smokers have profound differences in CVD risk factors related to their degree of insulin sensitivity. It is suggested that, in addition to smoking cessation efforts, attention should be given to identifying the subgroup of smokers most at risk for CVD, but unwilling or unable to stop smoking, and to initiating appropriate therapeutic interventions to decrease CVD in this high-risk group.

1. Introduction

Smoking is a major risk factor for atherosclerosis and cardiovascular disease (CVD), with a dose-response correlation between CVD morbidity and mortality and the number of cigarettes smoked [1]. Despite the fact that this relationship is well recognized, the recent report [2] from investigators of the INTERHEART study indicates that the overall population-attributable risk for current smoking was 38% in this worldwide study of the relationship between tobacco use and myocardial infarction. In a comment accompanying the INTERHEART study, Rosner and Stampfer [3] state that these results "should stimulate a redoubling of our efforts to rid the planet of the scourge of smoking."

The INTERHEART study [2] also pointed out that much of the excess CVD risk decreased after a year or so in those individuals who stopped smoking, emphasizing that smoking cessation is the ideal solution to this problem. However, despite widespread awareness of the adverse effects of smoking, large numbers of individuals continue to smoke;

The authors have no potential conflicts of interest. The funding sources played no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the manuscript; and in the decision to submit the paper for publication.

* Corresponding author. Falk Cardiovascular Research Center, Stanford University School of Medicine, CA 94305, USA. Tel.: +1 650 724 0954; fax: +1 650 725 1599.

E-mail address: fahim@stanford.edu (F. Abbasi).

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doi:10.1016/j.metabol.2008.03.016

Table 1
Baseline characteristics of the 2 study groups

Characteristic	IR (n = 19)	IS (n = 17)	*P* value
SSPG (mmol/L)	10.99 ± 2.13	3.99 ± 0.93	<.001
Age (y)	50 ± 9	49 ± 7	.85
Sex (male/female)	13/6	6/11	.09
BMI (kg/m^2)	29.8 ± 3.4	24.7 ± 4.1	<.001
Pack-years of smoking*	32 ± 14	33 ± 23	.82

Data are expressed as mean ± SD or number of subjects.

* Pack-years of smoking was calculated by multiplying the number of packs of cigarettes smoked per day by the number of years the person had smoked.

and the problem is compounded by the fact that the greatest health burden of smoking is borne by those individuals with lower socioeconomic status [4]. Given the obvious difficulties in relying entirely on smoking cessation to decrease CVD risk in tobacco users, it seems reasonable to ask if there are alternative approaches that might be of clinical utility in those individuals who either cannot, or will not, stop smoking. The present study was initiated to address this issue, and the results to be presented demonstrate that it is the insulin-resistant subgroup of smokers that is at greatest CVD risk and that administration of a thiazolidinedione compound significantly decreases the CVD risk factors in these individuals.

2. Subjects and methods

The study sample consisted of 36 apparently healthy cigarette smokers, selected from a total number of 85 smokers who responded to print advertisements describing our research interest in the relationship between smoking and CVD. General eligibility criteria included being between 30 and 70 years of age; in apparent good health; a history of smoking a minimum of 10 cigarettes per day for at least 5 years; without a desire to stop smoking; taking no medications known to affect glucose, insulin, or lipoprotein metabolism; and the stated willingness to participate in a 3-month intervention trial. Potential participants meeting these criteria were further evaluated by medical history, physical examination, and routine clinical laboratory measurements to exclude individuals with apparent disease and laboratory evidence of type 2 diabetes mellitus, anemia, or abnormal liver and kidney function. Individuals continuing to meet the eligibility criteria and still willing to volunteer for this study were scheduled for admission to the General Clinical Research Center of the Stanford University Medical Center. This study was approved by the Stanford Human Subjects Committee, and each subject gave written informed consent.

Insulin-mediated glucose disposal was quantified by a modified version [5] of the insulin suppression test as described and validated by our research group [6,7]. After an overnight fast, an intravenous catheter was placed in each arm of the subject, one for the simultaneous 180-minute infusion of octreotide (0.27 μg/m^2 per minute), insulin (32 mU/m^2 per minute), and glucose (267 mg/m^2 per minute) and the other for the collection of blood samples every 10 minutes during the 150- to 180-minute period to measure plasma glucose and insulin concentrations. Values obtained during the last 30 minutes were averaged to determine the steady-state plasma glucose (SSPG) and insulin concentrations. Because steady-state plasma insulin concentrations are comparable in all individuals and the glucose infusion rate is the same, the resultant SSPG concentration provides a direct measure of the ability of insulin to mediate the disposal of a given glucose load, that is, the higher the SSPG concentration, the more insulin resistant the individual. For the purpose of this study, individuals with an SSPG concentration ≥8.5 mmol/L were defined as *insulin resistant* (IR), whereas those with an SSPG concentration ≤5.5 mmol/L were classified as *insulin sensitive* (IS). Of the 85 volunteers, 30 (35%) met the IR criteria and 35 (41%) were classified as IS; and 19 and 17 of these individuals, respectively, were willing to enter the treatment phase.

The clinical and demographic characteristics of the 2 experimental groups are seen in Table 1. By selection, the mean SSPG concentrations were approximately 3 times higher in the IR individuals. In addition, the average body mass index (BMI) and the proportion of male volunteers were also greater in the IR group. However, the 2 groups were not different in terms of age and duration of smoking.

After creation of the 2 study groups, the following additional CVD risk factors were determined before starting the drug intervention part of the study.

2.1. Daylong metabolic meal profile

Plasma glucose, insulin, and free fatty acid (FFA) concentrations were measured as previously described [8] at hourly intervals for 8 hours after standard test meals containing, as percentage of daily calories, 15% protein, 42% carbohydrate, and 43% fat. Meals were given at 8:00 AM and 12:00 PM, containing 20% and 40%, respectively, of the estimated daily caloric intake.

2.2. Lipid and lipoprotein concentrations

Plasma samples obtained after an overnight fast on the morning of the insulin suppression test were stored frozen at −80°C until lipoprotein analysis by the vertical auto profile II method [9]. This method is a comprehensive lipoprotein profile testing design that directly measures high-density lipoprotein $(HDL)_2$ cholesterol, HDL_3 cholesterol, intermediate-density lipoprotein cholesterol, low-density lipoprotein cholesterol (LDL-C), very low-density lipoprotein cholesterol, and lipoprotein (a) in a single test. This method also provides a specific measure of narrow-density LDL-C, in contrast to the commonly measured LDL-C defined by the National Cholesterol Education Program, which includes both lipoprotein (a) and intermediate-density lipoprotein

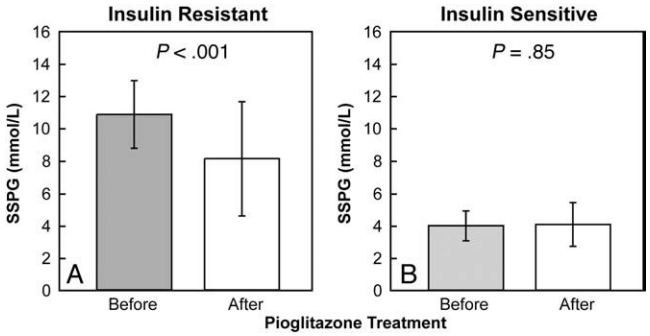

Fig. 1. Effect of pioglitazone treatment on mean ± SD SSPG concentrations in the IR and IS cigarette smokers. Within each group, the effect of pioglitazone treatment was evaluated by Student paired *t* test.

cholesterol. In vertical auto profile II, the narrow-density LDL-C subclass pattern is further evaluated by determining the LDL peak maximum time, that is, the relative position of the LDL peak in the density gradient on a relative scale of 0 to 200 seconds, with 0 second corresponding to the beginning of the HDL (the most dense lipoprotein) peak and 200 seconds corresponding to the very low-density lipoprotein (the least dense lipoprotein) peak maximum. Therefore, a patient with predominantly small, dense LDL has lower LDL peak maximum time compared with the LDL peak maximum time of a patient with predominantly large, buoyant LDL. Thus, the LDL pattern A (predominantly large and buoyant LDL subclass) is defined by an LDL maximum time >118 seconds, the LDL pattern B by an LDL maximum

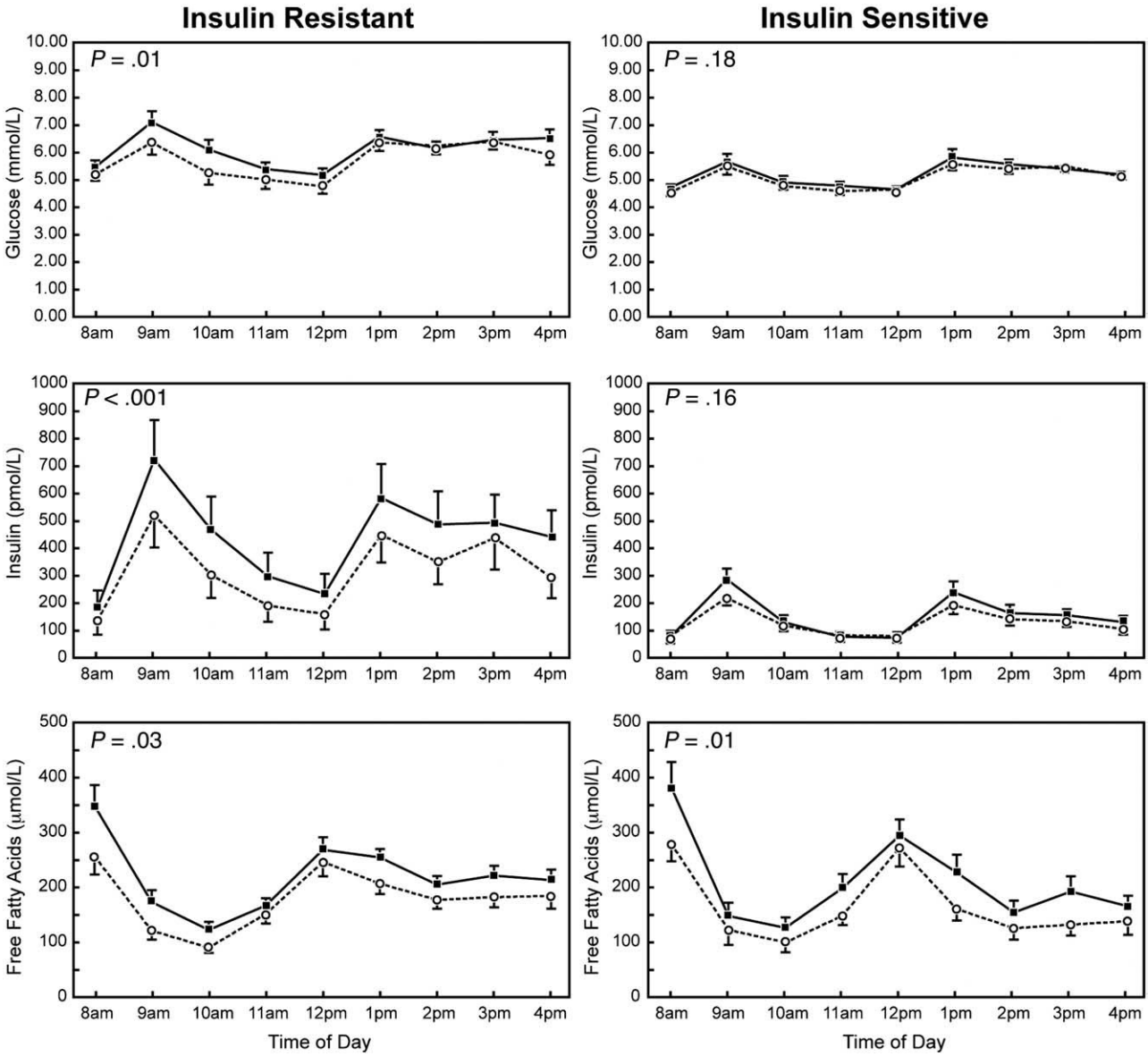

Fig. 2. Mean (SEM) daylong plasma glucose (upper panel), insulin (middle panel), and FFA (lower panel) levels before (■) and after (○) pioglitazone treatment in the IR and IS smokers. Subjects ate breakfast at 8:00 am and lunch at 12:00 pm. Within each group, the effect of pioglitazone treatment was evaluated by comparing the baseline and posttreatment AUCs by Student paired *t* test.

Table 2
Comparison of baseline lipid and lipoprotein, soluble adhesion molecule, and CRP concentrations in IR and IS smokers

Variable	IR	IS	P*	$P^{\dagger}$
TC (mmol/L)	4.38 ± 0.85	4.71 ± 0.51	.18	.31
LDL-C (mmol/L)	2.68 ± 0.66	2.93 ± 0.54	.23	.34
HDL-C (mmol/L)	1.01 ± 0.26	1.27 ± 0.29	.006	.03
HDL_2-C (mmol/L)	0.22 ± 0.12	0.32 ± 0.11	.02	.29
HDL_3-C (mmol/L)	0.78 ± 0.16	0.96 ± 0.19	.005	.01
Non–HDL-C (mmol/L)	3.38 ± 0.68	3.43 ± 0.59	.8	.75
TC/HDL-C ratio	4.4 ± 0.7	3.9 ± 1.0	.05	.10
TG (mmol/L)	2.51 ± 2.10	0.97 ± 0.26	<.001	.007
TG/HDL-C ratio	6.5 ± 7.1	1.9 ± 0.8	<.001	.002
LDL pattern (A/AB/B)‡	8/2/9	13/3/1	.02	–
sICAM-1 (ng/mL)	273 ± 95	278 ± 143	.51	.78
sVCAM-1 (ng/mL)	632 ± 414	625 ± 271	.52	.82
sE-selectin (ng/mL)	36 ± 18	30 ± 17	.37	.49
CRP (mg/L)	2.30 ± 2.42	2.03 ± 1.7	.89	.33

Data are reported as mean ± SD or number of subjects. LDL pattern A refers to large buoyant; AB, intermediate density; and B, small dense LDL particles.

* P values are for the comparison of 2 groups by Student unpaired t test.

† P values are for the comparison of the 2 groups by analysis of covariance (adjusting for differences in sex distribution and baseline BMI).

‡ The LDL pattern distribution of the 2 groups was compared by Fisher exact test and therefore not adjusted for sex and BMI.

time ≤115 seconds, and the intermediate pattern (AB) by an LDL maximum time >115 to ≤118 seconds.

2.3. C-reactive protein and soluble adhesion molecule measurements

C-reactive protein (CRP), soluble intercellular adhesion molecule 1 (sICAM-1), soluble vascular cell adhesion molecule 1 (sVCAM-1), and soluble E-selectin (sE-selectin) levels were measured by previously described assays [10].

After the baseline experimental measurements, pioglitazone treatment was initiated at a dose of 15 mg/d for the first 2 weeks. Volunteers were seen every 2 weeks and weighed, and their progress was discussed with one of the investigators. At the end of 2 weeks, the dose of pioglitazone was increased to 30 mg/d for the next 2 weeks, followed by 45 mg/d for 8 weeks. All participants were instructed to maintain their physical activity level for the duration of the study. Plasma alanine aminotransferase levels were checked at the end of each month, and the daily dose of pioglitazone was only increased in the presence of continued normal liver function. Liver function did not deteriorate in any of the 36 volunteers studied, and they all completed the treatment period without any adverse events. At the completion of the study, the reported physical activity level of the subjects was not significantly different from the baseline.

Data were analyzed using SPSS software, version 15.0 for Windows (SPSS, Chicago, IL) and SAS software, version 9.1 for Windows (SAS Institute, Cary, NC). Summary statistics are expressed as mean ± SD or number of subjects. The following variables were log-transformed to improve normality for statistical analyses: glucose, insulin, FFA, triglyceride (TG), TG to HDL cholesterol (HDL-C) concentration ratio, sVCAM-1, and CRP. Daylong glucose, insulin, and FFA responses to meals were evaluated by calculating their area under the curves (AUCs) by the trapezoidal method. Baseline characteristics of the 2 groups were compared by Student unpaired t test (continuous variables) and the Fisher exact test (categorical variables). Baseline CVD risk factors in the IR and IS groups were also compared by analysis of covariance adjusting for differences in sex distribution and baseline BMI. Within each group, treatment-related changes in continuous variables were assessed by Student paired t test, and the effect of pioglitazone treatment on LDL pattern distribution was evaluated by Wilcoxon signed rank (exact) test.

3. Results

There were no clinical problems associated with the administration of pioglitazone, and all of the volunteers completed the study without any adverse experiences. Both pioglitazone-treated groups gained a modest amount of weight during the study, with a somewhat greater change in the IS group (1.3 ± 2.2 kg, P = .03) as compared with the IR group (0.95 ± 2.8 kg, P = .15).

By selection, baseline SSPG concentrations were much higher in the IR group (10.99 ± 2.13 vs 3.99 ± 0.93 mmol/L, P < .001). As seen in Fig. 1, SSPG concentrations decreased significantly after pioglitazone treatment in the IR individuals (−2.74 ± 2.69 mmol/L, P < .001), whereas they remained essentially unchanged in the IS volunteers (0.08 ± 1.71 mmol/L, P = .85).

Fig. 2 illustrates daylong plasma glucose, insulin, and FFA concentrations in the IR and IS groups before and after pioglitazone treatment. Baseline plasma glucose concentrations (upper panel) were modestly but significantly higher in the IR group as compared with the IS group (glucose AUC, 48.81 ± 8.45 vs 41.83 ± 3.39 mmol/[L 8 h], respectively; P = .005). After administration of pioglitazone, daylong glucose levels significantly decreased in the IR group (48.81 ± 8.45 vs 45.78 ± 9.83 mmol/[L 8 h], P = .01), whereas they remained basically unchanged in the IS group (41.83 ± 3.39 vs 40.89 ± 3.26 mmol/[L 8 h], P = .18). Furthermore, before starting pioglitazone, daylong insulin concentrations (middle panel) were much higher in the IR group as compared with the IS group (insulin AUC, 3559 ± 3319 vs 1208 ± 622 pmol/[L 8 h], respectively; P < .001). After the treatment, daylong insulin levels declined significantly in the IR group (3559 ± 3319 vs 2586 ± 2633 pmol/[L 8 h], P < .001), whereas they did not change significantly in the IS group (1208 ± 622 vs 1034 ± 668 pmol/[L 8 h], P = .16). It should be noted that the effect of pioglitazone treatment on daylong insulin levels mirrored its effect on the SSPG concentrations in both groups. Finally, daylong FFA concentrations (lower panel) were similar at baseline in the IR and IS groups (FFA AUC, 1678 ± 435 vs 1617 ± 387 μmol/[L 8 h], respectively; P = .70); and after pioglitazone administration, they

Table 3
Effect of pioglitazone treatment on lipid and lipoprotein, soluble adhesion molecule, and CRP concentrations in the 2 study groups

Variable	IR			IS		
	Before	After	*P*	Before	After	*P*
TC (mmol/L)	4.38 ± 0.85	4.33 ± 0.84	.51	4.71 ± 0.51	4.70 ± 0.50	.94
LDL-C (mmol/L)	2.68 ± 0.66	2.63 ± 0.72	.56	2.93 ± 0.54	2.79 ± 0.40	.29
HDL-C (mmol/L)	1.01 ± 0.26	1.10 ± 0.30	.03	1.27 ± 0.29	1.42 ± 0.36	.004
HDL_2-C (mmol/L)	0.22 ± 0.12	0.25 ± 0.14	.11	0.32 ± 0.11	0.37 ± 0.17	.02
HDL_3-C (mmol/L)	0.78 ± 0.16	0.86 ± 0.19	.03	0.96 ± 0.19	1.05 ± 0.21	.007
Non–HDL-C (mmol/L)	3.38 ± 0.68	3.23 ± 0.70	.11	3.43 ± 0.59	3.28 ± 0.46	.23
TC/HDL-C ratio	4.4 ± 0.7	4.1 ± 0.8	.002	3.9 ± 1.0	3.5 ± 0.8	.002
TG (mmol/L)	2.51 ± 2.10	1.92 ± 1.18	.03	0.97 ± 0.26	1.01 ± 0.46	.98
TG/HDL-C ratio	6.5 ± 7.1	4.4 ± 3.3	.01	1.9 ± 0.8	1.7 ± 0.9	.35
LDL pattern (A/AB/B)	8/2/9	8/4/6 *	.75	13/3/1	15/2/0	.25
sICAM-1 (ng/mL)	273 ± 95	251 ± 77	.01	278 ± 143	263 ± 130	.02
sVCAM-1 (ng/mL)	632 ± 414	607 ± 405	.40	625 ± 271	641 ± 278	.75
sE-selectin (ng/mL)	36 ± 18	35 ± 23	.79	30 ± 17	30 ± 22	.99
CRP (mg/L)	2.30 ± 2.42	1.31 ± 1.44	.02	2.03 ± 1.7	1.22 ± 0.71	.07

Data are expressed as mean ± SD or number of subjects. Within each group, before- and after-treatment means were compared by Student paired *t* test; and LDL pattern distribution was compared by Wilcoxon signed rank test.

* One subject had missing LDL pattern data.

significantly decreased in both the IR (1678 ± 435 vs 1378 ± 437 μmol/[L 8 h], $P = .03$) and the IS (1617 ± 387 vs 1271 ± 406 μmol/[L 8 h], $P = .01$) groups.

Table 2 shows the baseline fasting plasma lipid and lipoprotein, soluble adhesion molecule, and CRP concentrations of the 2 study groups. In comparison to the IS group, the IR group had significantly higher plasma TG and lower HDL and HDL_3 cholesterol levels. In addition, the IR group had significantly higher TG/HDL-C concentration ratio as compared with the IS group. Furthermore, these differences continued to be statistically significant after adjustment for differences in sex and BMI. The IR group also had higher total cholesterol (TC) to HDL-C concentration ratio and lower HDL_2 cholesterol levels as compared with the IS group; however, these differences were not statistically significant after adjustment for differences in sex and BMI. Although there were no significant differences in the total, LDL, and non-HDL cholesterol concentrations between the 2 groups, the IR group had a significantly higher percentage of subjects with the less buoyant (pattern B) LDL particles. Finally, there were no significant differences in sICAM-1, sVCAM-1, sE-selectin, and CRP concentrations between the IR and IS groups both before and after adjustment for differences in sex and BMI.

Table 3 depicts the fasting lipid and lipoprotein concentrations and nonconventional cardiovascular risk factors in the 2 study groups before and after pioglitazone treatment. There were no changes in the total, LDL, and non-HDL cholesterol levels in the IR or IS groups. On the other hand, HDL-C concentrations increased significantly in both the IR and IS groups. This increase in HDL-C was also reflected by an increase in the HDL_3 cholesterol and a significant decrement in the TC/HDL-C concentration ratio. The HDL_2 cholesterol levels also increased in both groups; however, this increase was statistically significant only in the IS group. Triglyceride concentrations decreased significantly in the IR group, whereas they remained essentially unchanged in the IS group. Similarly, the TG/HDL-C concentration ratio significantly decreased in the IR group, whereas it did not significantly change in the IS group. Furthermore, after pioglitazone treatment, the LDL subclass pattern shifted toward more buoyant particles in both the IR and the IS groups; but this shift was not statistically significant in either group. Finally, sICAM-1 and CRP concentrations also decreased in both groups in association with administration of pioglitazone; however, the decrease in CRP in the IS group did not reach the conventional statistical significance of .05. There were no significant changes in the sVCAM-1 and sE-selectin levels after pioglitazone treatment in either group.

4. Discussion

Perhaps the most clinically relevant findings of this study are that approximately 35% of the smokers who volunteered for this study fell into the IR category. In addition, IR smokers displayed the CVD risk profile known to be associated with this defect in insulin action. Thus, they had higher daylong plasma glucose and insulin concentrations, an atherogenic lipoprotein profile characterized by higher TG and lower HDL-C concentrations, as well as differences in HDL-C subclasses. Parenthetically, it seems likely that results of previous studies [11-13] demonstrating that smokers have higher TG and lower HDL-C concentrations than nonsmokers may be related to the increased prevalence of insulin resistance and its characteristic dyslipidemia [14] in a population of smokers.

The results outlined above indicate that not only is the IR subgroup of smokers at greatly increased CVD risk, these

smokers represent a substantial proportion of the smoking population. Because the volunteers for this study were self-selected on the basis of an announced desire to continue smoking, this manner of recruitment may have affected the prevalence of smokers who were also IR. Furthermore, the experimental variables measured in this study may not be the only contributors to the increased prevalence of CVD in smokers. Although this is likely to be true, the difference in the lipid profile of IR and IS smokers cannot be lightly dismissed in view of the findings in the Copenhagen Male Study [15] that the incidence of CVD disease was not increased in smokers as long as they were in the third of the population with the lowest TG and highest HDL-C concentrations. In contrast, smokers in the third of the population with the highest TG and lowest HDL-C concentrations composed the group at the highest risk for CVD. Thus, given the magnitude of the enhanced CVD risk in IR smokers, it can be concluded that heart disease risk is not the same in all smokers.

The findings of our study suggest that at least one third of a group of cigarette smokers, who apparently intend to continue smoking, are significantly insulin resistant and that these individuals comprise the population of smokers at greatest CVD risk. Although the distinctions made in this article between smokers on the basis of their degree of insulin sensitivity and associated CVD risk appear to be quite dramatic, it could be argued that they are of little clinical relevance, as the goal should be to have everyone stop smoking; and this message should not be diluted by focusing on subgroup differences in CVD risk factors. Alternatively, the data presented might serve as the basis of 3 clinically relevant suggestions. At the simplest level, it would be important for some other research group to see if CVD risk is significantly enhanced in the subset of smokers who are also insulin resistant. Secondly, in light of the atherogenic lipoprotein profile in IR smokers, it would seem reasonable to screen all smokers for these abnormalities and, if present, initiate appropriate pharmacological intervention. For example, results of the Helsinki Heart Study [16] and the Veterans Affairs HDL-C Intervention Trial [17,18] have shown that CVD disease was significantly decreased in gemfibrozil-treated patients with high TG and low HDL-C concentrations: the dyslipidemic changes seen in IR smokers. Furthermore, in the Veterans Affairs study, the greatest clinical benefit of gemfibrozil treatment occurred in those subjects who were the most insulin resistant [18]. Parenthetically, we have suggested that having a plasma TG/HDL-C concentration ratio in milligrams per deciliter ≥ 3.0 is predictive of insulin resistance [19]; and it was of interest in this study that 16 of the 19 IR subjects met that criterion, whereas only 1 of those classified as IS did.

The third, and most contentious, issue is whether an effort should be made to identify IR smokers and treat them with an insulin-sensitizing agent. The results presented show that pioglitazone treatment is able to enhance insulin sensitivity in IR smokers, who continue to smoke, as well as improve CVD risk factors associated with insulin resistance. Indeed, the benefits of pioglitazone treatment were not entirely confined to IR smokers, as HDL-C concentrations significantly increased and CRP concentrations also decreased in pioglitazone-treated IS smokers. However, as significant as the metabolic benefits may be, there are no prospective data indicating that CVD outcomes can be improved by treating insulin resistance per se. On the other hand, given evidence that CVD risk varies in smokers as a function of degree of insulin sensitivity, and the large numbers of individuals unable or unwilling to stop smoking, it seems that it would not be out of the question to conduct a prospective trial with insulin-sensitizing drugs to see if CVD could be reduced in IR smokers who do not plan to stop smoking.

Acknowledgment

This study was supported in part by the National Institutes of Health (RR-000070), California Tobacco Related Disease Research Program (12RT-0159), and Takeda Pharmaceuticals North America.

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