Gemfibrozil Reduces Plasma C-Reactive Protein Levels in Abdominally Obese Men With the Atherogenic Dyslipidemia of the Metabolic Syndrome

To the Editor:

Recent data from Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial (VA-HIT) have recently reported that pharmacological treatment with a fibrate (gemfibrozil) significantly reduced coronary heart disease (CHD) risk among men with a history of CHD who had low HDL-cholesterol and LDL-cholesterol levels at baseline evaluation.[1] Moreover, this study also demonstrated that changes in the lipoprotein-lipid profile only partially explained the beneficial effect of gemfibrozil on CHD risk, suggesting that other factors may be responsible for the reduction in the risk of CHD observed among patients undergoing fibrate therapy.[2]

On the other hand, the contribution of inflammation to the development of atherosclerosis and CHD is increasingly recognized, and recent studies have identified some inflammatory markers, such as plasma C-reactive protein (CRP) and cytokines, as CHD risk factors.[3,4] Recent data have suggested that statins and fibrates may favorably decrease markers of inflammation.[5–8]

However, the effect of fibrates among abdominally obese men with the atherogenic dyslipidemia of the metabolic syndrome (a condition associated with markedly elevated inflammatory markers) has, to the best of our knowledge, never been reported. Thus, the aim of the present study was to examine the effect of a 6-month fibrate treatment on plasma CRP concentrations and cytokine levels such as interleukin (IL)-6 and tumor necrosis factor (TNF)-α in a sample of abdominally obese men with the atherogenic dyslipidemia of the metabolic syndrome.

Abdominally obese subjects (n=31 per treatment group) of the present study were asymptomatic volunteers who were between 25 and 55 years of age with a body mass index (BMI) between 27 and 40 kg/m^2 and a waist-to-hip ratio $\geq$0.95, as previously described.[9] Subjects received placebo or gemfibrozil (600 mg twice a day) for a period of 6 months. The study was approved by the Medical Ethics Committee of Laval University. Anthropometric as well as laboratory measurements were performed by using standardized techniques, as previously described.[9] Measurement of CRP levels was obtained with a highly sensitive immunoassay which used a monoclonal antibody coated to polystyrene particles (hs-CRP) performed on the Behring BN-100 nephelometer (Dade Behring). Cytokine levels were measured with an immunoassay by using monoclonal antibodies specific for human TNF-α and IL-6.

Both treatment groups showed small but statistically significant reductions in weight, BMI, waist circumference, and visceral adipose tissue accumulation ($P<0.05$). Although decreases in total cholesterol and apolipoprotein B concentrations were significant for both groups after the 6-month period, the magnitude of changes was greater in the gemfibrozil group as compared with placebo ($P<0.03$). Moreover, significant changes in triglyceride (-1.08 ± 0.89 mmol/L, $P<0.0001$; -36.8%) and HDL-cholesterol ($+0.08\pm0.10$ mmol/L, $P<0.0001$; $+9.48\%$) levels as well as in the cholesterol/HDL-cholesterol ratio (-1.12 ± 1.19, $P<0.0001$; -16.5%) were observed with only gemfibrozil treatment ($P<0.0001$).

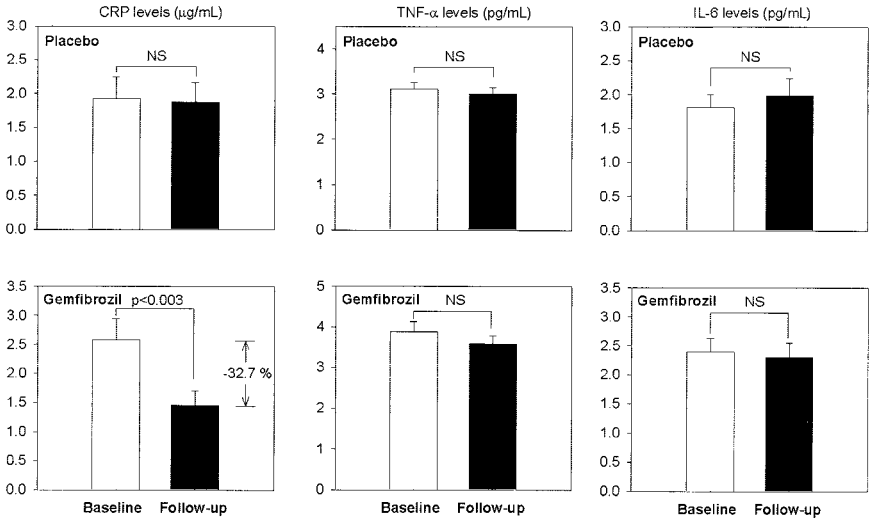
The effects of 6-month placebo or gemfibrozil treatment on plasma CRP and TNF-α or IL-6 levels are shown in the Figure. Plasma CRP concentrations were significantly reduced by only gemfibrozil therapy (-32.7%) (2.58 ± 1.99 vs 1.46 ± 1.19 μg/mL, $P<0.003$ for baseline and follow-up values, respectively). Furthermore, the change in the gemfibrozil group was significantly greater than in the placebo arm ($P<0.01$). However, neither TNF-α nor IL-6 levels were significantly reduced by gemfibrozil therapy.

Atherosclerosis is recognized to have an inflammatory component. In that sense, plasma CRP levels have been found to be predictive of cardiac events,[10] to be associated with elevated BMI and with a high abdominal fat accumulation[10,11] as well as to be related to the high triglyceride–low HDL-cholesterol dyslipidemia.[10] Finally, plasma CRP has been reported to be significantly reduced by hypolipidemic drugs.[5,7,8,12]

In this regard, studies have reported the beneficial effects of statin therapy on CRP levels.[5,12] Fibrates have also been shown not only to improve the high triglyceride–low HDL-cholesterol dyslipidemic state[1,9,13] but also to reduce CHD risk[1] and decrease plasma CRP levels.[7,8] In the present study, gemfibrozil treatment produced significant reductions in CRP levels. To the best of our knowledge, it is the first study to demonstrate that gemfibrozil therapy can favorably alter CRP concentrations among abdominally obese dyslipidemic patients with the features of the metabolic syndrome.

Circulating levels of TNF-α and IL-6 have been shown to stimulate the production of CRP.[14] Accordingly, it has been demonstrated that bezafibrate therapy reduced the production capacity of these two cytokines as well as CRP concentrations.[8] However, in the present study, gemfibrozil did not appear to affect the production of these cytokines, suggesting that this drug may rather alter the effect of IL-6 and TNF-α on CRP production. There are discrepancies in the literature regarding the impact of fibrates on CRP and cytokine levels and the type of patients as well as duration of trials may partly contribute to explain such differences.

In vitro studies have shown that fibrates have pleiotropic effects including the reduction of the inflammation process at the level of the vascular wall.[15] Fibric acids such as gemfibrozil are PPARα ligands that



Effect of a 6-month gemfibrozil treatment on plasma CRP, TNF-α, or IL-6 levels in a sample of abdominally obese men with the atherogenic dyslipidemia of the metabolic syndrome.

inhibit the progressive formation of atherosclerosis lesions,[15] which also involves the inflammatory component.[16] Thus, fibrates may reduce/slow atherosclerosis development not only through their hypolipidemic properties but also by decreasing the inflammation of the vascular wall.[17]

In summary, these results suggest that the beneficial effect of gemfibrozil on plasma CRP levels could represent another mechanism by which fibric acids may favorably reduce CHD risk by improving the low chronic inflammation state of abdominally obese dyslipidemic patients with the atherogenic dyslipidemia of the metabolic syndrome. Moreover, this positive effect was not mediated by changes in the concentrations of some inflammatory cytokines potentially regulating the production of CRP. Whether this effect of gemfibrozil on CRP plays a role in explaining the favorable impact of this fibric acid on CHD events among low HDL-cholesterol patients with type 2 diabetes or the metabolic syndrome[18] will require further studies.

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1. Rubins HB, Robins SJ, Collins D, et al. Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol: Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial Study Group. *N Engl J Med*. 1999;341:410–418.
2. Robins SJ, Collins D, Wittes JT, et al. Relation of gemfibrozil treatment and lipid levels with major coronary events: VA-HIT—a randomized controlled trial. *JAMA*. 2001;285:1585–1591.
3. Mendall MA, Patel P, Asante M, et al. Relation of serum cytokine concentrations to cardiovascular risk factors and coronary heart disease. *Heart*. 1997;78:273–277.
4. Ridker PM, Rifai N, Pfeffer M, et al. Elevation of tumor necrosis factor-alpha and increased risk of recurrent coronary events after myocardial infarction. *Circulation*. 2000;101:2149–2153.
5. Albert MA, Danielson E, Rifai N, Ridker PM. Effect of statin therapy on C-reactive protein levels: the pravastatin inflammation/CRP evaluation (PRINCE): a randomized trial and cohort study. *JAMA*. 2001; 286:64–70.
6. Rezaie-Majd A, Maca T, Bucek RA, et al. Simvastatin reduces expression of cytokines interleukin-6, interleukin-8, and monocyte chemoattractant protein-1 in circulating monocytes from hypercholesterolemic patients. *Arterioscler Thromb Vasc Biol*. 2002;22:1194–1199.
7. Staels B, Koenig W, Habib A, et al. Activation of human aortic smooth-muscle cells is inhibited by PPARalpha but not by PPARgamma activators. *Nature*. 1998;393:790–793.
8. Jonkers IJ, Mohrschladt MF, Westendorp RG, van der Laarse A, Smelt AH. Severe hypertriglyceridemia with insulin resistance is associated with systemic inflammation: reversal with bezafibrate therapy in a randomized controlled trial. *Am J Med*. 2002;112:275–280.
9. Dumont M, Mauriège P, Bergeron J, Després JP, Prud'homme D. Effect of a six month gemfibrozil treatment and dietary recommendations on the metabolic risk profile of visceral obese men. *Int J Obes Relat Metab Disord*. 2001;25:1136–1143.
10. Mendall MA, Patel P, Ballam L, Strachan D, Northfield TC. C reactive protein and its relation to cardiovascular risk factors: a population based cross sectional study. *BMJ*. 1996;312:1061–1065.
11. Lemieux I, Pascot A, Prud'homme D, et al. Elevated C-reactive protein: another component of the atherothrombotic profile of abdominal obesity. *Arterioscler Thromb Vasc Biol*. 2001;21:961–967.
12. Ridker PM, Rifai N, Pfeffer MA, Sacks F, Braunwald E. Long-term effects of pravastatin on plasma concentration of C-reactive protein: The Cholesterol and Recurrent Events (CARE) Investigators. *Circulation*. 1999;100: 230–235.
13. Saku K, Gartside PS, Hynd BH, Kashyap ML. Mechanisms of action of gemfibrozil on lipoprotein metabolism. *J Clin Invest*. 1985;75:1702–1712.
14. Baumann H, Gauldie J. Regulation of hepatic acute phase plasma protein genes by hepatocyte stimulating factors and other mediators of inflammation. *Mol Biol Med*. 1990;7:147–159.
15. Staels B, Dallongeville J, Auwerx J, et al. Mechanism of action of fibrates on lipid and lipoprotein metabolism. *Circulation*. 1998;98:2088–2093.
16. Ross R. The pathogenesis of atherosclerosis: a perspective for the 1990s. *Nature*. 1993;362:801–809.
17. Ericsson CG, Hamsten A, Nilsson J, et al. Angiographic assessment of effects of bezafibrate on progression of coronary artery disease in young male postinfarction patients. *Lancet*. 1996;347:849–853.
18. Rubins HB, Robins SJ, Collins D, et al. Diabetes, plasma insulin, and cardiovascular disease: subgroup analysis from the Department of Veterans Affairs high-density lipoprotein intervention trial (VA-HIT). *Arch Intern Med*. 2002;162:2597–2604.

IgG Is Higher in South Asians Than Europeans: Does Infection Contribute to Ethnic Variation In Cardiovascular Disease?

To the Editor:

Coronary heart disease (CHD) mortality is 40% higher in UK residents born in the Indian subcontinent than in the general UK population, a difference not explained by traditional cardiovascular risk factors. The burden of chronic infections has been associated with increased risk of CHD,[1] and South Asians are likely to have a different lifetime exposure to infection than those of European origin. Serum gamma globulin (IgG) is a nonspecific measure of immune activation. Elevated levels have been associated with increased risk of myocardial infarction.[2]

We measured total IgG using quantitative enzyme linked immunosorbent assays (ELISA)[3] in stored sera from 302 European and 302 South Asian participants in the Newcastle Heart Project, a stratified population sample of men and women 25 to 74 years old in Newcastle on Tyne, UK.[4] The study was approved by the local ethics committee, and participants gave written informed consent. In a previous study, we measured C-reactive protein (CRP) using a highly sensitive method in a subsample of 100 South Asian participants.[5] Of those included in the present study, 35 also had measurements available for CRP. IgG was log transformed, and results are presented as geometric means.

The mean age (SD) of Europeans was 54.5 years (13.1) and of South Asians 50.1 (12.1). Geometric mean IgG (95% confidence interval [CI]) was 7.4 (6.7, 8.2) g/L among Europeans and 13.5 (12.1, 15.2) g/L among all South Asians: 13.9 (11.4, 17.0) among Indians, 14.0 (11.8, 16.5) among Pakistanis, and 11.9 (9.2, 15.3) among Bangladeshis. Although levels were lowest among current smokers, IgG was higher in South Asians than in Europeans in each smoking category and in Indian, Pakistani, and Bangladeshi groups (Table). Adjusted for age, sex, and smoking status, geometric mean IgG was 75% higher (95% CI 48, 108) in South Asians.

Among 35 South Asian subjects (17 female) with information about CRP levels, there was a correlation ($r=0.48$, $P=0.003$) between log CRP and log total IgG.

Higher levels of total IgG have been reported in US blacks compared with whites,[6] although the difference (30%) was much smaller than the one we report here. This and the findings we report are both consistent with the hypothesis that people with ancestral origins in tropical environments have experienced genetic selection for increased pro-inflammatory responses.[7] The association between IgG and CRP in the small number of subjects with both measures available links raised IgG

Geometric Mean (95% CI) Total IgG (g/L) and Number

	European Whites		South Asians*		Indians		Pakistanis		Bangladeshis	
	Mean (CI)	No.	Mean (CI)	No.	Mean (CI)	No.	Mean (CI)	No.	Mean (CI)	No.
Men										
All	7.2 (6.3,8.2)	141	12.4 (10.5,14.6)	134	12.0 (8.8,16.4)	44	14.1 (11.2,17.7)	62	9.6 (6.4,14.4)	28
Nonsmokers	9.5 (6.9,13.1)	32	12.8 (9.9,16.6)	58	13.6 (8.8,20.9)	29	11.8 (8.4,16.6)	26	14.3 (0.9,238.2)	3
Exsmokers	7.0 (5.8,8.3)	67	13.6 (8.9,20.7)	26	7.3 (1.6,33.1)	5	17.4 (10.6,28.5)	17	10.4 (1.9,55.4)	4
Current smokers	6.2 (4.7,8.0)	41	11.1 (8.3,14.7)	46	10.7 (6.8,16.7)	8	14.5 (9.1,23.2)	18	8.8 (5.3,14.5)	20
Women										
All	7.6 (6.6,8.7)	153	14.6 (12.5,17.1)	163	15.2 (11.8,19.8)	72	13.8 (10.8,17.7)	66	15.0 (11.0,20.5)	25
Nonsmokers	7.8 (6.4,9.5)	61	14.7 (12.6,17.3)	151	15.2 (11.8,19.8)	72	14.5 (11.3,18.6)	59	13.7 (10.0,18.8)	20
Exsmokers	7.9 (6.0,10.4)	47	...	0	...	0	...	0	...	0
Current smokers	6.9 (5.3,9.1)	44	11.3 (1.0,132.3)	3	...	0	11.3 (1.0,132.3)	3	...	0
Men and women†	7.6 (6.8,8.4)	300	13.2 (11.8,14.8)	289	13.3 (11.1,15.9)	117	14.0 (11.8,16.5)	124	11.5 (8.8,15.0)	48

Totals in each smoking category do not sum to the total for each sex because of cases with missing information about smoking.
*Totals for Indians, Pakistanis, and Bangladeshis are included in the total for South Asians.
†Adjusted for age, sex, and smoking status using linear regression.

in this population to an established marker of CHD risk. We have also previously reported raised levels of leukocytes in Bangladeshis compared with Europeans.[4]

We found substantially higher levels of IgG in South Asians compared with Europeans, a difference not explained by factors known to be associated with IgG levels. This may reflect genetic differences, different exposures to infection, or ethnic differences in inflammatory processes. This finding is consistent with and could lend support to the hypothesis that the cumulative burden of infection is relevant to the excess of CHD in UK South Asians and requires confirmation from further studies.

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1. Prasad A, Zhu J, Halcox JPJ, Waclawiw MA, Epstein SE, Quyyumi AA. Predisposition to atherosclerosis by infections: role of endothelial dysfunction. *Circulation*. 2002;106:184–190.
2. Kervinen H, Palosuo T, Manninen V, Tenkanen L, Vaarala O, Manttari M. Joint effects of C-reactive protein and other risk factors on acute coronary events. *Am Heart J*. 2001;141:580–585.
3. Alkout A, Ramsay E, Blackwell C, Bentley A, Elton R, Weir D, Busuttil A. IgG levels to *Helicobacter pylori* among individuals who died of ischaemic heart disease compared to patients who experienced a first heart attack. *FEMS Immunol Med Microbiol*. 2000;29:271–274.
4. Bhopal R, Unwin N, White M, Yallop J, Walker L, Alberti K, Harland J, Patel S, Ahmad N, Turner C, Watson W, Kulkarni A, Laker M. Heterogeneity of coronary heart disease risk factors in Indian, Pakistani, Bangladeshi and European origin populations: cross sectional study. *BMJ*. 1999;319:215–220.
5. Fischbacher C, Bhopal R, Todd T, Walker D, Bignardi G. Consider ethnic variations. http://www.bmj.com/cgi/eletters/321/7255/208. Accessed March 18, 2003.
6. Tollerud D, Brown L, Blattner W, Weiss S, Maloney E, Kurman C, Nelson D, Hoover R. Racial differences in serum immunoglobulin levels: relationship to cigarette smoking, T-cell subsets, and soluble interleukin-2 receptors. *J Clin Lab Anal*. 1995;9:37–41.
7. Le Souef P, Goldblatt J, Lynch N. Evolutionary adaptation of inflammatory immune responses in human beings. *Lancet*. 2000;356:242–44.

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