

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/m² and a waist-to-hip ratio ≥ 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 ($+0.08 \pm 0.10$ 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 ($P < 0.0001$).

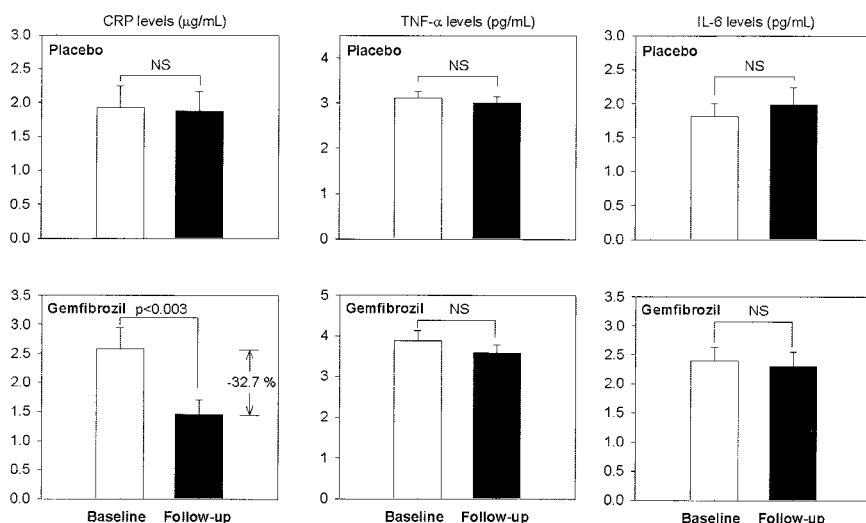
The effects of 6-month placebo or gemfibrozil treatment on plasma CRP and TNF- α or IL-6 levels are shown in the Figure. Plasma CRP concentrations were significantly reduced by only gemfibrozil therapy (-32.7%) (2.58 ± 1.99 vs 1.46 ± 1.19 $\mu\text{g/mL}$, $P < 0.003$ for baseline and follow-up values, 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 risk¹ 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 Fibrates such as gemfibrozil are PPAR α 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 syndrome¹⁸ will require further studies.

Acknowledgments

This study was supported by Parke-Davis/Warner-Lambert Canada Inc. Jean-Pierre Després is chair professor of Human Nutrition, Lipidology and Prevention of Cardiovascular Disease, supported in part by Pfizer, Proviso and the Foundation of the Québec Heart Institute; Jean Bergeron is a clinical research scholar from the Fonds de la Recherche en Santé du Québec.

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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.

Acknowledgments

We thank all contributors to and those acknowledged in the study reported in our Reference 4 and Dr Ananda Amarasinghe for help with study administration. We acknowledge financial support from the Barclay Trust, the British Diabetic Association, Newcastle Health Authority, the research and development directorate of the former Northern Regional Health Authority, the UK Department of Health, and the British Heart Foundation. Analysis of the serum samples was supported by a grant from the Gruss Bequest to Medical Microbiology, University of Edinburgh.

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Arteriosclerosis, Thrombosis, and Vascular Biology



JOURNAL OF THE AMERICAN HEART ASSOCIATION

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Arterioscler Thromb Vasc Biol. 2003;23:703-704

doi: 10.1161/01.ATV.0000060449.70345.8E

Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

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Print ISSN: 1079-5642. Online ISSN: 1524-4636

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