ARIC Manuscript Proposal # 869

PC Reviewed: 03/12/02	**Status: __A__**	**Priority: __1__**
SC Reviewed: 03/19/02	**Status: __A___**	**Priority: __1__**

1.a. Full Title: Plasma MCP-1 Concentration and Risk for Coronary Heart Disease (CHD)

b. Abbreviated Title (Length 26 characters): MCP-1 and incident CHD

2. Writing Group (list individual with lead responsibility first):

Lead: Ron Hoogeveen
Address: Baylor College of Medicine
Department of Medicine, Mail Station:F701
6565 Fannin Street
Houston, TX 77030
Phone: (713) 798-3407 Fax: (713) 798-7400
E-mail: ronh@bcm.tmc.edu

Writing group members: Christie Ballantyne
Eric Boerwinkle
Molly Bray
Alanna Morrison
Charles Etta Rhodes
Richey Sharrett

3. Timeline: All sample analyses have been completed by the Lipid Laboratory. Statistical analysis will start February, 2002 and manuscript will be completed by July 2002.

4. Rationale:

The hypothesis that atherosclerosis is an inflammatory disease is supported by both the discovery of inflammatory cells in the cap of atherosclerotic plaques and recent reports that elevated levels of plasma markers of inflammation are associated with incidence of CHD (Ross, 1999). Atherosclerosis begins with the adherence of monocytes to the activated endothelium and progresses with the formation of lipid-laden foam cells that are characteristic of early atherosclerotic lesions. Monocyte chemoattractant protein-1 (MCP-1), a member of the chemokine family of chemotactic cytokines, is involved in the pathogenesis of atherosclerosis by promoting recruitment of inflammatory cells to the vessel wall (Rossi and Zlotnik, 2000).

A variety of cell types, including monocytes, vascular endothelial cells, and smooth muscle cells, produce MCP-1 in response to inflammatory cytokines such as IL-1β, IL-4, TNF-α, and IFN-γ. Incubation with minimally modified LDL also leads to increased MCP-1 production in vascular endothelial cells and smooth muscle cells (Cushing et al., 1990). Furthermore, MCP-1 expression is upregulated in macrophage-rich areas of atherosclerotic

lesions compared to nonlesional areas of the vessel (Nelken et al., 1991; Wilcox et al., 1994).

MCP-1 signals through its cognate receptor, the chemokine receptor 2 (CCR2), and a significant correlation between plasma LDL levels and CCR2 expression has been found in hypercholesterolemic patients, but not in normolipidemic subjects, suggesting that MCP-1 may possibly be a molecular link between LDL-cholesterol and foam cell formation (Han et al., 1999).

Although a large number of studies have focused on the potential role of MCP-1 in the pathogenesis of atherosclerosis, only a few prospective studies have investigated the relationship between circulating plasma levels of MCP-1 and incidence of CHD. A recent study showed that plasma MCP-1 levels were significantly higher in 20 patients with hyperlipoproteinemia IIa or IIb compared to 23 normolipidemic subjects (Kowalski et al., 2001). In addition, a study of 405 healthy Japanese subjects showed that age and serum triglyceride were significant predictors of plasma MCP-1 concentration in men (Inadera et al., 1999). In women, age was also a predictor of MCP-1 concentration, but serum triglyceride was not correlated with circulating MCP-1 levels. However, this study also found that plasma MCP-1 concentrations from 24 patients with CHD were not significantly different from age-matched, normal controls.

In summary, to date there is very limited data available on the relationship of plasma MCP-1 levels and incidence of CHD. Therefore, we propose to investigate the association of plasma levels of MCP-1 with incident CHD.

References:

Cushing SD, Berliner JA, Valente AJ, *et al*. Minimally modified low density lipoprotein induces monocyte chemotactic protein 1 in human endothelial cells and smooth muscle cells. Proc. Natl. Acad. Sci. USA 1990; 87: 5134-5138.

Han KH, Han KO, Green SR, Quehenberger O. Expression of the monocyte chemoattractant protein-1 receptor CCR2 is increased in hypercholesterolemia: differential effects of plasma lipoproteins on monocyte function. J. Lipid Res. 1999; 40:1053-1063.

Inadera H, Egashira K, Takemoto M, Ouchi Y, Matsushima K. Increase in circulating levels of monocyte chemoattractant protein-1 with aging. J. Interferon Cytokine Res. 1999; 19:1179-1182.

Kowalski J, Okopien B, Madej A, Makowiecka K, Zielinski M, Kalina Z, Herman ZS. Levels of sICAM-1, sVCAM-1 and MCP-1 in patients with hyperlipoproteinemia IIa and -IIb. Int. J. Clin. Pharmacol. Ther. 2001; 39:48-52.

Nelken NA, Coughlin SR, Gordon D, Wilcox JN. Monocyte chemoattractant protein-1 in human atheromatous plaques. J. Clin. Invest. 1991; 88:1121-1127.

Ross R. Atherosclerosis—an inflammatory disease. N Engl J Med 1999;340:115-126.

Rossi D, Zlotnik A. The biology of chemokines and their receptors. Annu. Rev. Immunol. 2000; 18:217-242.

Wilcox JN, Nelken NA, Coughlin SR, *et al*. Local expression of inflammatory cytokines in human atherosclerotic plaques. J. Atheroscler. Thromb. 1994; 1(suppl 1): S10-S13.

5. Main Hypothesis/Study Questions:

Increased plasma levels of MCP-1 are associated with increased risk for CHD events and PAD, as well as increased carotid artery thickness.

Secondary hypotheses are that increased levels of LDL-cholesterol are associated with increased plasma levels of MCP-1 and that plasma MCP-1 is associated with markers of inflammation (WBC, VCAM-1, ICAM-1, CRP, fibrinogen, E-selectin, L-selectin, P-selectin)

6. Data (variables, time window, source, inclusions/exclusions):

MCP-1 measurements were made on Visit 1 plasma samples of CHD cases, cohort stratified random sample (CRS), PAD, African American, MRI, and 3-group**.**
Data will include incident CHD case status and date of CHD diagnosis.
Covariates will include visit 1 age, gender, race, center, BMI, years of cigarette smoking, incident diabetes, triglycerides, LDL cholesterol, HDL cholesterol, treatment with statins, inflammatory markers (WBC, ICAM-1, VCAM-1, fibrinogen, CRP, E-selectin, L-selectin, P-selectin).

7.a. Will the data be used for non-CVD analysis in this manuscript? ____ Yes _X___ No

b. If Yes, is the author aware that the file ICTDER02 must be used to exclude persons with a value RES_OTH = "CVD Research" for non-DNA analysis, and for DNA analysis RES_DNA = "CVD Research" would be used? ____ Yes ____ No
(This file ICTDER02 has been distributed to ARIC PIs, and contains the responses to consent updates related to stored sample use for research.)

8.a. Will the DNA data be used in this manuscript? ____ Yes _X___ No

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER02 must be used to exclude those with value RES_DNA = "No use/storage DNA"? ____ Yes ____ No

9. The lead author of this manuscript proposal has reviewed the list of existing ARIC Study manuscript proposals and has found no overlap between this proposal and previously approved manuscript proposals either published or still in active status.
ARIC Investigators have access to the publications lists under the Study Members Area of the web site at: http://bios.unc.edu/units/cscc/ARIC/stdy/studymem.html

____X__ Yes _____ No