

Hostility, anger, and depression predict increases in C3 over a 10-year period

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Abstract

We examined the relation of hostility, anger, and depression to 10-year changes in the third (C3), and fourth (C4) complement in 313, apparently healthy male participants enrolled in the Air Force Health Study (AFHS), a 20-year study designed to evaluate the health consequences of dioxin exposure. Hostility, depression, and anger were assessed using subscales from the Minnesota Multiphasic Personality Inventory (MMPI), which was administered in 1985. Given the high intercorrelations among these psychological scales, we used a principal component analysis to generate a composite score representing the linear combination of the hostility, anger, and depression scales. The dependent variables, C3 and C4 levels, were determined from samples collected in 1992, 1997, and 2002. Regression analyses controlling for age, race, alcohol use, body mass index, and cigarette use as well as onset of disease, and use of lipid lowering and blood pressure medications during follow-up revealed a significant time \times composite score interaction for C3 complement ($p < .0003$), but not C4. Post-hoc analyses revealed that high composite scores were associated with larger 10-year increases in C3. These observations suggest that men who are hostile and are prone to experience frequent and intense feelings of anger, and depression show activation of the complement system, and specifically increases in C3, that may contribute to the development of coronary heart disease.

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1. Introduction

Epidemiological evidence continues to support the psychosomatic hypothesis that hostility, anger, and depression are associated with an increased risk of atherosclerotic cardiovascular disease (ACVD) (e.g., Ahmad, 2000; Ferketich et al., 2000), Type 2 diabetes (T2D) (Arroyo et al., 2004), and essential hypertension (EH) (Everson et al., 1998). Although the mechanisms accounting for those associations are not well delineated, one emerging hypothesis posits that psychological attributes contributes to adverse health via inflammation (Black, 2003). Support for this hypothesis comes from a number of cross-sectional studies that have reported significant associations between bio-

markers of inflammation, such as interleukin (IL)-6, tumor necrosis factor (TNF)- α , and C-reactive protein (CRP), and anger (Suarez, 2004), hostility (Graham et al., 2006; Suarez, 2003a), and depression (e.g., Miller et al., 2002; Suarez et al., 2003), as well as to a composite score representing the linear combination of those variables (Suarez, 2003b, 2004). While compelling, the cross-sectional nature of those prior observations limits any conclusions regarding prospective associations. If inflammation is an important pathophysiological mechanism whereby psychological attributes contribute to the development and progression of chronic diseases, it is critical to demonstrate that individuals characterized by high levels of hostility, anger, and depression exhibit increasing or elevated levels of inflammatory biomarkers over time.

One aspect of the immune system that has been associated with ACVD and T2D is the complement system. While there are a number of components to the immune complement

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system (Ritchie et al., 2004), studies investigating its role in the development of chronic diseases have focused on the major protein C3, and to a lesser extent, C4. The emphasis placed on C3 is due, in part, to its production by activated macrophages and its role as a cytokine (Zimmer et al., 1982), and its control of lipid and glucose metabolism (Baldo et al., 1993), pathways leading to cardiovascular disease and diabetes. C4, on the other hand, has been linked with obesity and glucose metabolism (Engstrom et al., 2005). Cross-sectional studies have shown that C3 is associated not only with risk factors of CHD (Onat et al., 2005) and diabetes (Engstrom et al., 2005), but also with the presence and severity of CAD (Figueredo et al., 1993; Ylitalo et al., 1997), and ischemic stroke (Di Napoli et al., 2001). In one prospective study, C3, but not C4, was associated with incident T2D (Engstrom et al., 2005). C3 has also been associated with incident myocardial infarction (Muscarelli et al., 1995) and incident atrial fibrillation (Dernellis and Panaretou, 2006).

Only a few studies have examined the relation of psychological attributes and/or psychological stress to activation of the complement system. Elevations in C3 and C4 have been noted in depressed patients in some (Berk et al., 1997; Kronfol and House, 1989; Song et al., 1994), but not all (Spivak et al., 1989) studies. Other studies have shown that the stress of academic examination evokes increases in C3c, but only among those students who perceived the examination as stressful, whereas C4 showed a significant reduction in students with low-stress perception (Maes et al., 1997). Although few in number, the findings of the previous studies suggest that psychological attributes, and emotional stress are associated with activation of the complement system.

To date, no study has examined the relation of the complement system to anger and hostility or has examined these potential associations over time. The aim of the present study, therefore, was to examine the relation of psychological risk factors to changes in serum levels of C3 and C4 over a 10-year period. In light of our previous cross-sectional observations (Suarez, 2004), we hypothesized that the linear combination of hostility, anger, and depression would be similarly associated with elevations in C3 and C4 levels, and with greater changes in these proteins over time.¹

2. Methods

2.1. Participants

The study sample consisted of men who participated in the Air Force Health Study (AFHS). A detailed description of the study design and the participant selection procedure has been published previously (Wolfe et al., 1990). Briefly, the AFHS was designed to evaluate the health of the veterans of Operation Ranch Hand, the unit responsible for the aerial

spraying of Agent Orange and other dioxin-contaminated herbicides in Vietnam from 1962 to 1971. Initially, all living Ranch Hands and a matched comparison group of Air Force veterans who served in Southeast Asia, but were not occupationally exposed to herbicides in Vietnam, were invited to participate in the 20-year study. Physical examinations were performed in 1982, 1985, 1987, 1992, 1997, and 2002. The examination content emphasized detection of medical endpoints suspected of being associated with exposure to dioxin, so extensive data on health status and health behaviors were collected. In 1985, the examination included a one-time administration of the Minnesota Multiphasic Personality Inventory (MMPI). The MMPI is a well-established self-report questionnaire that has been used to assess various dimensions of personality, and has been used in many studies examining the relation of psychological factors to risk of various chronic medical illnesses and stress-induced pathophysiological mechanisms. Assessment of C3 and C4 levels was included only in the 1992, 1997, and 2002 exams.

Of the participants in the AFHS, 2065 subjects completed the 1985 and 1992 examinations. From this total, participants were excluded if, in the 1992 assessment, they reported any of the following: use of anti-inflammatory medications including statins ($N=232$); history of liver disorders ($N=603$); myocardial infarction ($N=100$); diabetes ($N=265$); hypertension ($N=101$); cancer ($N=284$); HIV ($N=4$); drug ($N=5$) or alcohol dependence ($N=127$); and psychosis ($N=54$). Four hundred and ninety-five people had more than one of these conditions. An additional 41 participants were excluded because they were taking other medications suggestive of other chronic conditions (e.g., thyroid medication) or acute conditions that might have immunological consequences (e.g., penicillin). Lastly, participants that were missing data on one or more of the covariates ($N=10$) were also excluded. These relatively stringent exclusion criteria were implemented in order to evaluate the relation of psychological attributes to complement levels with less confounding from these conditions.

Of the remaining 598 people in the sample, 545 attended the 1997 examination and 519 attended the 2002 examination. Those participants that reported using anti-inflammatory medications at the 1997 ($N=80$) or 2002 ($N=178$) examinations were also excluded. Our study sample was composed of 313 (133 Ranch Hands) who met inclusion criteria and attended the 1985, 1992, 1997, and 2002 examinations.

In comparison to the study sample ($N=313$), (see Table 1 for means) those subjects who were excluded were older (mean = 54.53 year, $p < .0001$); less well educated; consumed more drinks of alcohol per day (mean = .76, $p < .04$); smoked more cigarettes per day (mean = 5.98, $p < .002$), and had higher body mass index (mean = 28.59 kg/m², $p < .0001$); depression (mean = 7.07, $p < .0001$); hostility (mean = 13.34, $p < .0003$); anger (mean = 3.72, $p < .0005$); C3 complement levels (mean = 120.07 mg/dl, $p < .0001$), and C4 complement levels (mean = 29.54 mg/dl, $p < .0001$). Ranch Hand status, racial composition, and level of physical activity did not significantly differ between the study sample and those subjects who were excluded ($p > .05$). Given this pattern of findings, individuals who were excluded would likely have the effect of attenuating the magnitude of the associations examined in these analyses. All of the participants were male (19 African Americans) with a mean age in 1992 of 50.16 years. (SD = 6.32). See Table 1 for a further description of study participants.

2.2. Measurement of psychological attributes

All participants were administered the 566-item MMPI at the 1985 examination. Assessment of hostility, anger, and depression was performed using MMPI-derived subscales. For the 14 subjects with missing items, we multiplied the mean of the completed items by the number of items making up that scale. Simulation studies have demonstrated that this approach to handling missing data yields relatively unbiased estimates and is a reasonable alternative to more complex approaches such as multiple imputation (Schafer and Graham, 2002).

2.2.1. Hostility

Hostility was assessed using 39-items from the Cook-Medley Hostility Scale (CMHS) (Cook and Medley, 1954) of the MMPI. These items, identified by Barefoot et al. (1989), reflect the cognitive (i.e., cynicism and

¹ As a corollary to the stated hypothesis, we also speculated that each of the individual components, that is, anger, hostility, and depression, would also predict changes in C3 and C4 over time.

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