Ethnicity differences in vascularity, obesity, and inflammatory biomarkers: A Pilot Study.

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ABSTRACT

The purpose of this pilot investigation was to assess the differences in cardiovascular risk factors between a healthy cohort of African Americans and Caucasians utilizing clinical and serum biomarkers with highly sensitive sonographic endothelial measures. Clinical biomarkers (body mass index, waist circumference, blood pressure, percent flow mediated dilation in the brachial artery); serum lipids (total, LDL and HDL cholesterol, and triglycerides); and obesity (leptin and adiponectin) and inflammatory biomarkers (C-reactive protein, IL-1β, IL-1RA, IL-2, IL-4, IL-5, IL-6, IL-6R, IL-8, IL-10, IFN- γ, TNF-α, TNF-RI, TNF-RII and GM-CSF) were assessed in 43 healthy individuals (22 African Americans, 21 Caucasians) between the ages of 20 and 55 with a mean age of 30.2 ±8.6.The clinical biomarkers demonstrated no significant differences between cohorts. Serum cholesterol (P = 0.06), TNF-α (p=0.06), and adiponectin (P = 0.09) levels were lower in African Americans. African Americans also demonstrated significantly lower levels of serum inflammatory biomarkers IL-2, IL-4, IFN- γ, GM-CSF, IL-6R, IL-1RA and TNF-RI ($p < 0.05$). Overall positive correlations were demonstrated between BMI and leptin and BMI and hsC-RP; and leptin and hsC-RP. Negative correlations were demonstrated between adiponectin and IL-6 and percent FMD and TNF-RI. Result s from this pilot study suggest that African Americans tend to have significantly lower levels of numerous serum inflammatory biomarkers as well as lower lipid (cholesterol) and obesity (adionectin) biomarkers relative to Caucasians, supporting future investigation in a larger trial.

Keywords

Cytokines; Marker, Biological; Cardioovascular Disease; Chiropractic; Ultrasonography; Group, Ethnic

LITERATURE REVIEW

Biomarkers

Leptin

Leptin is a hormone that functions in a feedback loop modulating adipose tissue mass[1]. During starvation leptin levels fall, activating a behavioral, hormonal, and metabolic response that is adaptive when energy stores are reduced. Weight gain increases plasma leptin concentration and elicits a different response leading to a state of negative energy balance[2]. Several clinical studies have demonstrated that high-leptin levels can help to predict acute CVD events and strokes.[3] In a SIRCA study (single-center, community-based, crosssectional study of factors associated with CAC, plasma leptin levels were directly associated with coronary artery calcification across genders.[4]

Adiponectin

Adiponectin is synthesized by the white adipose tissue and circulates at relatively high (2-20 mg/mL) serum concentrations.[5] The levels of adiponectin though are seen reduced in obesity[6,7], insulin resistance status[8,9], type 2 diabetes[10], and CAD[11,12]. There is inconclusive data on the association between adiponectin and coronary artery calcification[13] and is increasingly implemented as a marker for atherosclerotic disease, its decrease having been shown to be predictive of acute coronary syndrome, myocardial infarction, coronary artery disease, and ischemic cerebrovascular disease. Adiponectin augments endothelial nitrous oxide production, protecting the vasculature by reducing platelet aggregation and vasodilation. Adiponectin also

acts as an endogenous antithrombic factor and inhibits macrophage activation and foam cell accumulation[15].

C-Reactive Protein

C-reactive protein (CRP) is an acute-phase protein that appears in circulation in response to inflammatory cytokines, such as interleukin 6, and serves as a biomarker for systemic inflammation.[15,16]Elevated CRP levels are associated with cardiovascular disease [17]. C-reactive protein increases rapidly with the onset of tissue destruction or inflammatory stimuli[18]. Circulating CRP concentration is directly related to severity of heart failure in human patients[19], and is a strong predictor of adverse outcome in patients with acute cardiovascular diseases[20].

Interleukin 1β

IL-1β is produced during injury, inflammation, immunological challenge or infection, and contributes to the inflammatory response that may have an important effect on CNS diseases, such as multiple sclerosis and Alzheimer's disease[21]. IL-1β can provoke a cascade of pro-inflammatory events such as up-regulation of vascular adhesion molecules which can induce marked neutrophilic inflammation[22].

Interleukin 2

IL-2 has many cellular responses, including differentiation, anti-apoptosis, cytokine release and

potent proliferation of T lymphocytes, affecting both cytotoxic as well as regulatory T cells[23]. IL-2 aids in the differentiation of B cells into IgG cells, thus participating in T cell memory[24]. IL-2 increases the cytotoxic functions of T-killer cells and NK cells; it promotes the production of perforins and FN-gamma by T-killer and NK-cells as well as activiating monocytes and macrophages to secrete TNF-alpha, IL-1B, IL-6, IL-8, G-CSF and CM-CSF[25]. IL-2 also proliferates the inflammation cascade by stimulating NF-KB genes[26].

Interleukin 4

Interleukin-4 is a pleiotropic cytokine produced largely by activated Th2-polarized T-cells, mast cells and basophils. It acts upon a broad range of targets, including hematopoietic cells, endothelial cells and tumor cells (Vinarskaja 2012)[27].IL-4 also contributes independently to Th2-driven eosinophilic inflammation in asthma by binding to its type I receptor IL-4Ra/g and stimulating T-cellmaturation and Th2 skewing from Th0 cells, and by inhibiting Th2 lymphocyte apoptosis[28].

Interleukin 5

IL-5 is associated with eosinophil and basophil recruitment and degranulation in inflammation[29]. It is another cytokine produced by Th2 lymphocytes, eosinophils and mast cells, which has been shown to play amajor role in many allergic diseases through eosinophil activation[30]. IL-5 exerts its activity by binding to a heterodimeric receptor composed of an IL-5-specific a chain and a b chain that is common to granulocyte-macrophage colony-stimulating factor (GM-CSF) and IL-3

receptors[31].

Interleukin 6

IL-6 has different functions for acute-phase and chronic-phase inflammation [32]. It is produced not only by immune and immune accessory cells but also by many nonimmune cells and organs (such as osteoblasts and bone marrow stromal cells)[33-40]. At the onset of inflammation, IL-6 is released with tumor necrosis factor - alpha and IL-1[41]. IL-6 then inhibits tumor necrosis factor-alpha and IL-1[42], activates the production of acute-phase reactant from the liver[43], and stimulates the hypothalamic-pituitary-adrenal axis to control inflammation[44].

Interleukin 8

Interleukin 8 is known for its chemoattractant properties for neutrophils and T-lymphocytes [45,46]. It stimulated by IL-1 and TNF-a[47]. Along with IL-6 and TNF-a, IL-8 is produced by mononuclear macrophages and endotheliocytes involved in activating and inducing T cells, B cells, and natural killer cells to target and phagocytosize pathogenic cells (Figure 1). IL-8 enters cells by combining with the chemokine receptor CXCR1, to activate the extracellular ERK2/1 signaling pathway and promote the formation of new microvessels. [48]. One study suggested that IL-8 promotes leukin chemotaxis into tumors, leading to tumor neovascularization and the acceleration of tumor growth and metastasis [49].

Interleukin 10

IL-10 contributes to suppression of immunological and inflammatory responses[50]. IL-10 contributes to the inhibition of cell adhesion molecules, monocyte chemotactic protein-1, tissue factor, fibrinogen, matrix metalloproteinase-9, T-lumphocyte granulocyte-macrophage colony-stimulating factor, inducible nitric oxide synthase and smooth muscle cell proliferation [51-53]. IL-10 also inhibits the secretion of chemotactic proteins by macrophages that might attract further leukocytes to the location of subendothelial inflammation[54] (Figure 1). Moreover, IL-10 reduces the production of lytic enzymes produced by monocytes, such as matrix-metalloproteinases (enzymes associated with destabilization of a plaque), and suppresses superoxide anion production[55], suggesting that IL-10 could prevent plaque destabilization[56]. It has been suggested that IL-10 may arrest and reverse the chronic inflammatory response in established atherosclerosis as well as limit thrombotic complications [57].

Tumor Necrosis Factor-alpha

TNF-α is an inflammatory cytokine released when a cell is injured, infected, or is under an autoimmune response. Binding of TNF-α to the cell surface can signal a myriad of responses including apoptosis, growth, or the release of more cytokines/chemokines. When cytokines/chemokines are released, immune cells are signaled to the injury site; this sometimes results in inflammation [58].

Interferon-gamma

INFγ is a pro-inflammatory cytokine that activates neutrophils and macrophages [59]. With GM-CSF, INFγ induces the production of TNF-α and can enhance membrane molecule expression [60]. It is produced by TH1 and NK cells[61]. (Figure 1)

Granulocyte Macrophage-Colony Stimulating Factor

CM-CSF is a cytokine secreted in response to IL-1 and TNF-α by a variety of cells including endothelium, fibroblasts, muscle cells and macrophages. It is activated by T-cells [62]. GM-CSF regulates autoantigen-specific $CD4^+$ T cells indirectly through stimulation of IL-6 and IL-23 production by DC and macrophages in the presence of microbial products[63].

Role of Biomarkers and Cardiovascular Disease

Inflammatory biomarkers are increasingly held accountable for the progression and clinical outcome of atherosclerotic plaqueing[64]. The amount of IL-6 and its byproduct CRP are proportionate to the intensity of occult palque inflammation and have been thought to determine the probability of plaque rupture. Furthermore, the monocyte chemoattractant protein 1 (MCP-1) and IL-8 play a crucial role in initiating coronary artery disease by recruiting monocytes/macrophages to the vessel wall. This leads to the formation of atherosclerotic lesions and also increases the vulnerability of the plaque[65].

Adipose tissue contributes to cardiovascular disease as an endocrine organ[66]. White

adipose tissue, the main adipose tissue of adults, secretes many biologically active molecules such as leptin, tumor necrosis factor-α, and plasminogen-activator inhibitor type 1 which contribute to the development of cardiovascular disease and hypertension[67,68] (Figure 2).

Cardiovascular Disease

CVD has been recognized as the dominant cause of death in the United States for at least 50 years, with heart disease ranking first and stroke ranking third as specific causes of death. CVD accounts for >900 000 deaths annually in the United States; 12 million Americans have CHD, and another 4 million have had a stroke[69]. Atherosclerosis is a cardiovascular disease where atheromatous plaques develop on the endothelium of large and intermediate-sized arteries. Ateriosclerosis is a general thickening and stiffening of blood vessels of all sizes[70].

The current view of atherogenesis is a combination of the response to injury hypothesis wherein atherosclerosis is a chronic inflammatory response of the arterial wall to endothelial injury and the inflammation cascade [71].The development of atherosclerotic plaque begins with the attachement of monocytes and lipids to adhesion molecules on a damaged or dysfunctional endothelial cell of an artery. This initial attachement can be from cytokines such as tumor necrosis factor, mechanical denudation, hemodynamic forces, immunce complex deposition, irridation, or chemicals. The subsequent diapedesis of the monocytes into the tunica intima of the vessel wall is followed by the differentiation of monocytes into macrophages by the cytoking macrophage colony-stimulating factor [72]. The activated macrophage ingests and oxidizes the accumulated lipoproteins forming macrophage foam cells and releasing cytokines interferon gamma and interleukin 12 [73]. Foam cells then coalesce into a visible fatty streak. The fatty

streaks show in increase in elastin-containing polar amino acids that allows for the binding of calcium and connective tissue material forming plaques [74]. Eventually, the firbroblasts of the plaque deposit dense connective tissue that causes the arteries to become stiff. After this stiffness calcium salts will precipitate with the cholesterol and other lipids leading to bony calcifications [75].

Risk factors for cardiovascular disease cause structural and functional endothelial dysfunction [76]. Endothelium is a major regulator of vascular homeostasis, maintaining the balance between vasodilation and vasoconstriction, inhibition and stimulation of smooth muscle cell proliferation and migration, and thrombogenesis and fibrinolysis[77,78]. Blood pressure, total cholesterol, high-density lipoprotein cholesterol, smoking, glucose intolerance, and left ventricular hypertrophy are physiologic risk factors for cardiovascular disease[79]. There is also evidence for psychological stress factors elevating inflammation and causing endothelial dysfunction and cardiovascular disease including social isolation, depression, maladaptive coping styles, excessive alcohol consumption, and smoking[80].

Metabolic Syndrome

The National Education Program's Adult Treatment Panel III report identified the metabolic syndrome as a multiplex risk factor for cardiovascular disease with six main components: abdominal obesity, dyslipidemia, raised blood pressure, insulin resistance and/or glucose intolerance, proinflammatory state, and prothrombotic state[81]. Under this definition, 22% of US adults have metabolic syndrome. Little ethnic difference was found, with Caucasians having slightly higher prevalence than African Americans (23.8% and 21.6% respectively)[82].

Abdominal obesity, measured in waist circumference, especially correlates with metabolic risk factors (hypertension, high serum cholesterol, low HDL cholesterol, hyperglycemia, and increased cardiovascular disease risk). Excess adipose tissue releases fatty acids (NEFA), cytokines, PAI-1, and adiponectin which exacerbates cardiovascular risk factors. A high plasma NEFA level overloads muscle and liver with lipid, which enhances insulin resistance. High CRP levels accompanying obesity may signify cytokine excess and a proinflammatory state. An elevated PAI-1 contributes to a prothrombotic state, whereas low adiponectin levels that accompany obesity correlate with worsening of metabolic risk factors. The strong connection between obesity (especially abdominal obesity) and risk factors led some researchers to redefine metabolic syndrome as a clustering of metabolic complications of obesity[84].

The atherogenic dyslipidemias of Type II diabetes, the Metabolic Syndrome and mixed (IIB) hyperlipidemia feature moderate to marked elevation of triglyceride-rich lipoproteins, low HDL-C cholesterol levels, and a dense LDL phenotype; equally, they feature an inflammatory state. These risk factors also contribute to prematrue atherosclerosis and elevated cardiovascular risk[84].

Autonomic dysfunction may be a contributor to metabolic syndrome[85]. It is suggested that early changes in the neural control of cardiac activity may provide a potential mechanism mediating a pathophysiological link between impaired glucose tolerance and cardiovascular disease[86]. Obesity, hypertension, and insulin resistance are a few of the metabolic syndrome components that demonstrate an alteration in autonomic nervous system function[87]. Altered cardiac autonomic function precedes the presence of insulin resistance in metabolic syndrome[88] and may be associated with early glucose dysmetabolism leading to the development of

diabetes[89].

Ultrasound and Endothelial Dysfunction

The presence of atherosclerosis in the endothelium shows impairments in endothelium-dependent vasodilatation. Specifically, a paradoxical constriction in the arteries of patients with mild and advanced coronary artery disease is observed[90]. Furthermore, endothelial dysfunction can be detected with flow-mediated dilation at both the conduit and microvascular levels in patients with coronary risk factors but no ultrasound evidence of structural coronary artery disease confirming that endothelial dysfunction is present in the preclinical stages of atherosclerosis [91].

A non-invasive method of detecting endothelial dysfunction is to use high-resolution ultrasound to measure the brachial artery diameter in response to reactive hyperemia [91]. Reactive hyperemia increases blood flow and shear stress stimulating flow-mediated dilation that can be quantified as an index of vasomotor function[92,93,94]. The systemic nature of atherosclerosis is reflected by the close correlation between endothelial dysfunction in the forearm and coronary artery dysfunction[92,93]. Brachial flow-mediated dilation is a validated, noninvasive physiological measure widely used as a research tool to quantify endothelial functio[95].

The autonomic nervous system and inflammation

The autonomic nervous system (ANS) plays an essential role in the bidirectional relationship between the central nervous system and immune systems[96]. Elevated parasympathetic nervous

system activity is associated with attenuated immune system responsiveness to inflammatory stimuli [97]. Non-invasive markers of sympathovagal imbalance, particularly reduced HRV power and high-frequency HRV, are associated with higher concentrations of systemic inflammation markers such as IL-6, TNF-α, and fibrinogen. Some evidence exists demonstrating increased inflammation in depressed versus non-depressed individuals, but a common underlying factor of cardiovascular disease may explain the ambiguity[96]. Parasympathetic withdrawal and increased sympathetic activation is associated with increased cardiovascular mortality risk[98].

Antidromic dorsal root reflex can influcenc inflammation through recruitment of inclammatory cells and by triggering vasoactive edema[99]. The spinal cord receives input, then signals back to the periphery by antidromic action potentials via afferent fibers[100]. The first inflammatory events in neurogenic inflammation are arteriolar vasodilation, plasma extravasation, and hyperalgesia[101]. Additionally, microglial cells in the spinal cord play a role in inflammation. Cytokines and signaling pathways that mediate peripheral inflammation are also seen in the central nervous system during microglial activation, specifically mitogen-acivated protein kinases, IL-1 and TNF[102].

Syptathetic activation is pro-inflammatory[103]. Up-regulation of the sympathetic nervous system is involved in several cardiovascular disease processes and is responsible for alterations in normal myocardial structure and function, including the induction of arrhythmias, alterations in contractile properties and cardiac remodeling[104]. Inflammatory infiltrate into the heart occurs with elevated sympathetic nervous system activity, with changes seen in mast cells, macrophages, and T cells[105]. Other inflammatory cells express adrenergic receptors that either enhance or suppress cytokine production[106]. CRP and IL-6 are associated with autonomic dysfunction of the heard and are thought to promote the development of cardiovascular

disease[107].

Adipocytokine changes in response to neural stimuli is seen in several situations. In isolated adipocytes, β-stimulation increased IL-6[108] where β-blockers dampened the normal IL-6 increase response to stress in rats[109]. CRP and IL-6 are associated with diabetic polyneuropathy[110]. A shift of sympathovagal balance toward increased sympathetic activation have been associated with leptin mediation[111]. Additionally, the sympathetic nervous system has been shown to regulate adiponectin levels and its synthesis in white adipose tissue *in vivo*[112].

INTRODUCTION

Since the 1980's, coronary heart disease and stroke mortality rates differ among the major ethnic groups in the United States (Table1) (National Center for Health Statistics, personal communication, August 2000)[113]. African Americans have the highest rates of CHD (65% higher rate than Caucasians[114]), and non-Hispanic whites also have relatively high CHD mortality. Native Americans, Asians, and Hispanics have lower rates. CHD mortality rates are especially high in middle-aged black men relative to other race/sex groups, and stroke mortality rates are strikingly higher in blacks in general. Native Americans and Hispanics have the lowest stroke rates [115]. Fatal stroke, death from heart disease, congestive heart failure and end-stage kidney disease related to hypertension is disproportionately higher in African Americans[116].

	CHD	Stroke
Non-Hispanic white	182.8	60.3
Black	186.8	81.6
Native American	112.7	39.2
Asian	100.1	54.6
Hispanic	124.2	40.0

Figure 3. CHD and Stroke Mortality Rates by Race and Ethnicity in the United States in 1997. Data are expressed as mortality per 100 000 population and are based on rates age-adjusted to the 2000 standard; they are from the National Center for Health Statistics[115].

There are also disparities in how the CHD statistics have changed over the last thirty years. The rates of CHD mortality have declined more slowly in black men than in white men. Although white men at one time had higher age-adjusted (to the year 2000 standard) rates than black men, the rates are now almost identical. The declines in CHD mortality rates among black women have also been somewhat slower than among white women; black women have had higher rates since the mid-1980s[115]. (Figure 3)

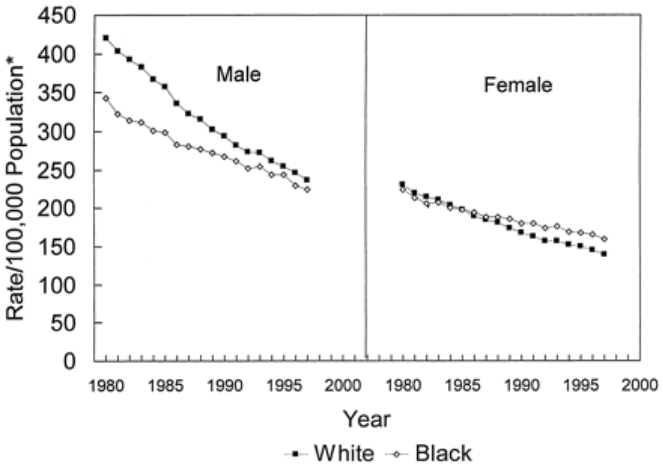

Figure 3. Death rates for coronary heart disease by sex and race in the United States from 1980 to 1997. *Rates are age-adjusted to 2000 standard[115].

There are several proposed reasons for disparities within cardiovascular disease mortality. First, there is a disparity in socio-economic status[116]. When measured by education, income, or

occupation disparities in CVD mortality are observed [117,118]. Data from US metropolitan areas show a graded relationship between income inequality and heart disease mortality[119].

Poorer access to health care has also been suggested as a source of disparity[116, 120]. Rooks et all (2008) report that older African American had significantly worse health care than their counterpart white adults; one-third of Black men (32.9%) and women (30.5%) had no supplemental health insurance compared with 5.7% and 4.2% of Caucasian men and women, respectively. Similarly, more than one-third of African American men (35.7%) did not report a regular source of care through a HMO or private doctor, followed by about one-fourth of African-American women (23.8%), in contrast to less than ten percent of Caucasian men (9.4%) and women (9.6%)[121].

Modifiable risk factors (hypertension, diabetes, obesity, hypercholesterolemia, smoking, and lack of leisure-time physical activity) are also suggested sources for disparity[122]. After adjusting for health care and SES, racial differences in hypertension as a possible source of cardiovascular disease were significantly higher in older African American men than Caucasian men[121]. The prevalence of overweight and obesity is higher in Hispanic men than in non-Hispanic white or black men and is higher in both black women and Hispanic women than in non-Hispanic white women[118]. The prevalence of hypertension was high among blacks regardless of sex or educational status; the prevalence of hypercholesterolemia was generally high among Caucasian and Mexican American men and Caucasian women in both education groups; the prevalence of low concentrations of HDL cholesterol and hypertriglyceridemia was most favorable among African-American participants, although among the most educated women, Caucasians and African- Americans had a similar prevalence of low concentration of HDL cholesterol[123].

OBJECTIVES AND HYPOTHESIS

The purpose of this pilot investigation was to assess the differences in cardiovascular risk factors between a healthy cohort of African Americans and Caucasians utilizing clinical and serum biomarkers with highly sensitive sonographic endothelial measures. We hypothesized that African American ethnicity would be associated with increased vascular risk factors.

METHODS

Study population and protocol

The current study was approved by Logan College Institutional Review Board. A total of 43 healthy participants [22 African Americans (10 males, 11 females), 21 Caucasians (10 males, 12 females) aged from 20 to 55 years were recruited from the students, and faculty and staff members from the institution. A written informed consent was obtained from each participant and the race/ethnicity for a study participant was determined based on his/or her self-report. Individuals with systemic or collagen vascular disease (i.e. rheumatoid arthritis, progressive systemic sclerosis, ankylosing spondylitis, Marfan's, polyarteritis nodosa), heart disease, or stroke were excluded from our study. All subjects abstained from caffeine, exercise smoking, vitamin and mineral supplements, and caloric intake for at least 12 hours prior to study participation. Fasting blood sample was collected for each participant and vascular assessments (i.e. FMD, systolic and diastolic blood pressures) were performed on the same day the blood was drawn.

Sample analyses

Serum samples were frozen at -40 C and analyzed within 30 days after the blood collection. The Cytokine panel included 10 cytokines, IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10,

TNF-α, IFN-γ, and GM-CSF which were measured using an Invitrogen (Carlsbad, CA) magnetic high sensitivity 10 plex assay kit (LHC0001) and Luminex 200 plate reader. Also included in the serum analysis were IL-6R, IL-IRA, TNF-RI and TNF-RII.

Serum levels of leptin and adiponectin were assessed by double-antibody enzyme-linked immunosorbent assay (ELISA) (R&D Systems, Minneapolis, MN) according the manufacturer's specifications. The hsCRP, total and HDL cholesterol, and triglyceride assay was based on a latex particle-enhanced immunoturbidimetric method using a kit (Pointe Scientific Inc., Lincoln Park, MI) and a Cobas Mira Plus clinical autoanlyzer (Roche Diagnostics, Ltd, Rotkreutz, Switzerland). LDL cholesterol was calculated using the Friedewald calculation of total cholesterol - HDL - (triglycerides/5). The assay quality was assessed by 49 blinded controls from a pooled sample donated by 10 premenopausal volunteers.

Vascular assessments

The GE LOGIQ *e* (GE Healthcare, Milwaukee, WI) ultrasound unit with a broadband probe at 10 MHz was used to image all subjects and longitudinal images of the brachial artery were obtained. Pulse wave velocity was employed in order to confirm the presence of the brachial artery versus the brachial vein. A skilled single examiner performed all of the sonographic examinations. Flow mediated dilation was assessed by having the subjects positioned supine on a comfortable exam table in a quiet, temperature controlled room for 20 minutes prior to imaging of the brachial artery. The subjects' blood pressure was taken while supine. Once the imaging exam began, the subject, remained in the supine position with their extended, supinated right arm placed across a solid surface and parallel to the floor. A blood pressure cuff was placed around the subject's arm. To image the brachial artery proximal to the blood pressure cuff, the transducer was first placed on the brachial artery in transverse. The

transducer was then rotated 90 degrees in order to image the brachial artery longitudinally. Brachial artery location was confirmed by Power Doppler. One baseline image was taken of the brachial artery during maximal pulsation (diastole). The blood pressure cuff was then inflated to 50 mm Hg over the subject's systolic blood pressure. The blood pressure cuff remained inflated for 5 minutes. Approximately thirty seconds prior to deflation, the transducer was again placed on the brachial artery longitudinally. The cuff was deflated after 5 minutes of brachial artery occlusion and an image was again recorded. The diameter of the brachial artery was measured three times, pre and post occlusion from intima to intima. Post-occlusion diameter was obtained between 30 seconds and 200 seconds after release of the blood pressure cuff. The same examiner performed all of the measurements. Measurements of the brachial artery were obtained by using the ultrasound system's digital cursor which targeted the intima to intima measures providing precise diameter measurements.

Statistical analyses

Ethnicity groups (African-Americans vs. Caucasians) were assessed for comparability of characteristics by Fisher's exact test for categorical variables and analysis of variance (ANOVA) for continuous variables.

The General Linear Model (GLM) was used to examine differences in vascular parameters, and obesity and inflammatory biomarkers between African-Americans and Whites. A basic model and a full model with the adjustment of age (continuous), BMI (continuous), and sex were performed. Ethnicity differences in the above parameters were also examined using t-test after stratification by sex. Spearman correlation was used to assess the associations between analyte levels. SAS software (SAS Institute, Cary, NC) was used for analyses. All tests were 2-

sided, and $P < 0.05$ was considered statistically significant.

RESULTS

In our study, there were no significant differences in participant characteristics between African-Americans and Caucasians in the current study population (Table 1). The mean age of participants was 30.2 ± 8.6 (SD) years. A total of 46.5% were males and 53.5% were females and 23.3% were obese.

Body mass index (BMI) was positively correlated to CRP (r = 0.40, P = 0.008) and leptin (r = 0.44, P = 0.003). IL-6 was significantly correlated to IL-10 (r =0.40 , P = 0.007) and GM-CSF (r = 0.69, P < 0.0001) and inversely correlated to adiponectin (r = -0.34, P = 0.03). TNF-α was positive correlated to its receptors, TNF-receptor I (TNF-RI; r = 0.39, P = 0.01) and TNF-receptor II (TNF-RII, r = 0.28, P = 0.07).

Vascular assessments and serum lipid levels are shown in Table 2. Overall, African-Americans did not differ on parameters of vascular assessments [Flow mediated dilation (FMD), systolic and diastolic blood pressures], and serum triglyceride and HDL cholesterol levels from Caucasians. Serum levels of total and LDL cholesterol levels were lower in African-Americans than in Caucasians; however, the differences did not reach statistical significant probably due to our small sample size (total cholesterol, P = 0.06; LDL-cholesterol, P = 0.08).

Table 3 demonstrates serum obesity and inflammation related biomarkers among the two race/ethnic groups. African Americans had statistically significantly lower serum IL-2, IL-4, IFN-γ, GM-CSF, IL-6R, IL-1RA, and TNF-RI levels compared to Caucasians (Ps < 0.05). Serum IL-10 (P = 0.005) and TNF-α (P = 0.06) were also lower in African Americans. With respect to adipocytokines, borderline statistically significantly lower levels of serum adiponectin were

observed in African-Americans than in Caucasians. There were no overall significant differences in serum leptin, hsCRP. 1L-1β, IL-8, and TNF-RII levels. The average IL-6 levels in African-Americans (15.68 pg/mL) were approximately 74% higher than that in Caucasians (9.01 pg/mL); however, the difference was not statistically significant (P = 0.26) due to the relatively high statistical variations in the former group (African-Americans). Stratification by sex showed similar trends for the above vascular parameters (data not shown), serum lipids, and serum obesity and inflammatory markers except for IL-6 where a lower level was observed in African-American females (P = 0.14) (Table 4). In addition, the ethnic differences in IL-2 in females and TNF-α, IL-6R, IL-1RA, and TNF-RI in males reached statistical significances although the sample size within each strata became smaller (Table 4).

DISCUSSION

Biomarkers and Ethnic Differences

CRP levels have previously been reported as higher in African Americans than Caucasians. A series of prospective epidemiologic studies have shown that higher levels of CRP are associated with incident cardiac and vascular events in healthy men and women; recent clinical practice recommendations from the Centers for Disease Control and Prevention (CDC) and the American Heart Association (AHA) support the use of CRP testing in selected patients to help assess cardiovascular (CV) risk[124]. Our study showed no significant difference between CRP levels. CRP was positively correlated to BMI which is consistent with current literature[125].

IL-6 has previously been reported as higher in African Americans than non-Aftrican Americans, furthermore it is cited as one factor in the well documented racial and ethnic disparities in health[126]. Higher plasma IL-6 levels are associated with adverse health habits: values are higher in smokers than nonsmokers, in individuals who report less physical activity, in those whose sleep is impaired, and in those with a higher BMI, all behaviors that are adversely affected by stress[127].

This study did not find significant differences in IL-6 or CRP between Caucasians and African-Americans. IL-6 induces hepatic production of CRP, but the two markers act independently to influence cardiovascular health[128]. Ranjit et al (2007) found disparities between Caucasians and African-Americans in IL-6 and CRP; but at the same education level there were no significant differences between these biomarkers[129]. The results of this study come from a pool of mostly higher-educated participants – doctoral students and staff (many of which have higher education degrees). The education level of the participants may explain the lack of significance.

IL-6 was significantly related to IL-10, GM-CSF, and adiponectin. It previously has been shown that IL-10 effectively down-regulates proinflammatory cytokines, such as IL-1, IL-6, and TNF-α, its effects are not confined to these mediators. IL-10 also reduces the production of chemotactic factors, such as IL-8 or CC chemokines, that may attract further leukocytes to the location of inflammatory activity[130] explaining the connection between IL-6 and IL-10. One of the ways IL-6 promotes atherosclerosis is by decreasing adiponectin (an antiatherogenic adipokine) mRNA in vitro[131] which supports the inverse correlation between IL-6 and adiponectin in this study.

The results pertaining to insignificant IL-8 levels contrasts previous literature. Mayr et al found higher levels of IL-8 in Caucasian women then African-American women as did Grann et al[132,133]. Mada et all[134] has results similar to this study, but their mobidly obese population contrasts the overweight population of this study. IL-8 is released by adipocytes and is correlated with BMI. It is significantly higher in obese individuals than lean individuals[135]. The findings of this study suggest that BMI has a larger influence on IL-8 than ethnicity.

Previous studies which assessed ethnic differences (African-Americans vs. Caucasians) in inflammatory biomarkers mainly focused on CRP, IL-6, and TNF-α. [136-139] and the majority of these studies reported a higher CRP [136,137] and IL-6 levels[138] in African-Americans than Caucasians after controlling confounders such as socioeconomic and other health related variables. The discrepancies in CRP and IL-6 between the current and previous observations could be partially explained by the fact that our study population was younger (mean age, 30.2 ± 8.6 yr) and relatively healthy (no self-reported metabolic diseases). The current findings in TNF-α and TNF-R1 were consistent with the study by Hyatt et al.[139]who reported that Caucasians had greater intra-abdominal adipose tissue (IAAT), insulin sensitivity, and serum concentrations of TNF-α, TNF-R1, and TNF-R2 than African-Americans. The above researchers suggested that greater TNF-α in Caucasians vs. African-Americans was attributed to greater IAAT in whites since IAAT was in favor of TNF-α and IL-6 production[139]. Consistently, our results also suggested that serum IL-6 levels were likely to be lower in African-American females vs. their Caucasian counterparts.

In the current study, we observed that African-Americans had lower serum adiponectin levels compared with Caucasians which was in agreement with previous observations [139,140]. It is suggested that adiponectin may reduce the secretion of pro-inflammatory cytokines such as TNF-

α, thus alleviating the condition of atherosclerosis. However, it is unlikely that the lower levels of TNF-α observed in African-Americans vs. Caucasian in our study was attributed in part to ethnic differences in adiponectin. The serum levels of adiponectin are not statistically significant even though they are trending. Given the established inverse relationship between BMI and adiponectin[141]the results of this study suggest that BMI has a stronger influence on serum adiponectin levels than ethnicity.

Ethnic Differences in FMD and Blood Pressure

Although a significantly higher FMD was observed for Caucasian as opposed to African-American individuals previously, no significant difference in FMD and other vascular parameters such as systolic and diastolic blood pressures were found in our study.[142]

Ethnic Differences in Blood Lipids

While this study found no difference in HDL, LDL or total cholesterol levels, previous research has found African Americans to have higher HDL values and a lower total cholesterol to HDL ratio.[143] Most of the cholesterol marker research comparing ethnic groups is done with elderly patients over 65 years of age, which explains why the data in this study differs.

Strengths and Limitations

To our knowledge, this pilot study was the first to examine a relatively complete panel of

inflammatory cytokines among African-Americans vs. Caucasians. Since we focused on a younger (mean age: 30.2 ± 8.6 yr), healthier (no self-reported metabolic diseases), and well educated college population, our results were less likely to be confounded by other factors such as socioeconomic status and health related issues. The current study had limitations. Our sample size was limited and the study participants were conveniently recruited from the college community. Therefore, the results may not reflect the ethnic difference in general. In addition, we did not examine certain health related behaviors like smoking and alcohol consumption. However, our results are novel and biological plausible, suggesting that young, healthy, well-educated African -Americans had lower levels of most pro- and anti- inflammatory markers compared to their Caucasian counterparts.

The population of this study functions both as a strength and a limitation. Many of the participants are students of a younger age than many of the previous cytokine studies. The younger age group is not represented well in current cytokine literature, but the separate ethnic populations are matched for age and BMI. Additionally, Logan College of Chiropractic students tend to be more active than the general population and eat a different diet than the majority of the population. This is also a limitation of the study as a food frequency questionnaire was not administered to the students to see if their diet follows that of mainstream America and they did not report the time and intensity of their physical activity. The study did not only comprise of students; faculty and staff participated as well with a mean age closer to that of most of the literature reviewed in this paper.

Conclusion

Summary

The results of this pilot study suggested that overall, African Americans had significantly or borderline significantly lower levels of the majority of analyzed inflammatory cytokines compared to Causasians in the current sample of college students, faculty, and staff members. Lower levels of serum cholesterol and adiponectin were also observed in Afrian-Americans although the differences (African-Americans vs. Caucasians) were not statistically significant. Similar results were found across subgroups defined by sex.

For Further Study

Evidence exists where education affects obesity[144]. Evidence also exists that obesity affects cytokine levels[145-147]. While SES as a whole does not appear to influence cytokine levels[148], a study correlating education level to cytokine levels is warranted.

The psychological factors influencing inflammatory cytokines is another subject for further study. It is established that psychological factors influence the markers of cardiovascular disease for men more than for women[149], and that chronic stress alters immunity[150]. The psychological parameters that correlate with changes in inflammatory cytokines would be an interesting subject to study.

The relationship between chiropractic adjustments and autonomic regulation/dysregulation warrants further study. Heart rate variability is established as a measure

of the autonomic nervous system[151], and heart rate changes are associated with chiropractic adjustments[152]. It would be interesting to see if individuals under chiropractic care show a change in autonomic regulation (i.e. parasympathetic/sympathetic dominance) and to see if there is a resultant change in inflammatory cytokines as a result of chiropractic care.

POTENTIAL CLINICAL INTERVENTIONS

Regular endurance-oriented exercise training enhances insulin action and lowers an individual's risk for CVD [153]. Current evidence supports that aerobic exercise, alone or combined with hypocaloric diet, improves symptoms of metabolic syndrome – possibly altering systemic levels of adipokines. Physical activity leads to lower circulating levels of pro-inflammatory cytokines and higher levels of adiponectin[154].

Exercise alone has shown to increase serum adiponectin and decrease serum TNF-α concentration. When combined with a diet which increased fish, fiber and vegetable intake while decreasing refined carbohydrates additional decreases in leptin were observed (the decrease in leptin also reflected the decrease in fat mass of the participants)[155].

Omega-3 supplementation favorable modifies many adverse serum and tissue lipid alterations related to metabolic syndrome. There is a drastic reduction in fasting and postprandial serum triacylglycerols and free fatty acids observed with EPA and DHA supplementation both alone and in combination. Analysises suggest EPA enrichment in platelet phospholipids to be independently associated with serum triacyglycerol lowering. Reduced VLDL production in the liver both intra and extra-hepatically. Omega-3s have contrasting effects o f LDL, with a slight tendency to increase LDL-cholesterol concentrations. Additionally, omega-3 supplementation is associated with changes in cellular fatty acid partitioning (away

from triacylglycerol synthesis pathways and toward fat oxidation) and are thought to have favorable effects in subjects with metabolic syndrome by reducing ectopic fat deposition and associated organ lipotoxicity. Furthermore, omega-3's are shown to reduce inflammatory status, decrease platelet activation, mildly reduce blood pressure, improve endothelial function, and increase cellular antioxidant defense[156].

Figure 1: Biomarker interactions. Dark blue arrows represent products of upstream cytokines centered around the NF-KB gene. Light blue arrows represent cytokines that work synergistically to promote a downstream effect. Green arrows demonstrate facilitative factors; red arrows represent inhibitory factors. Yellow circles are adipokine influences in this cascade.

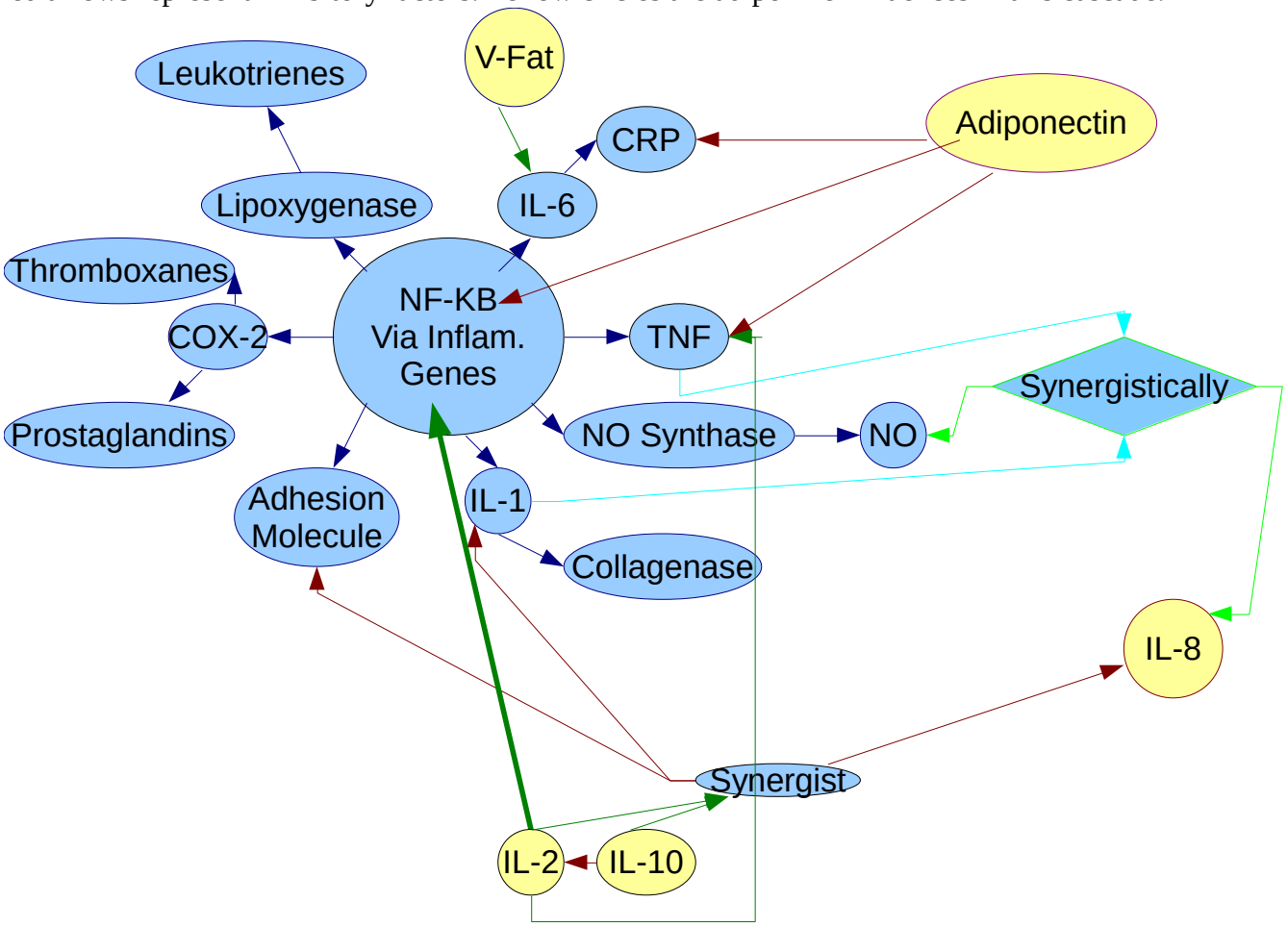

Figure 2. Adipocytokines and their anti/pro inflammatory effects.[64]

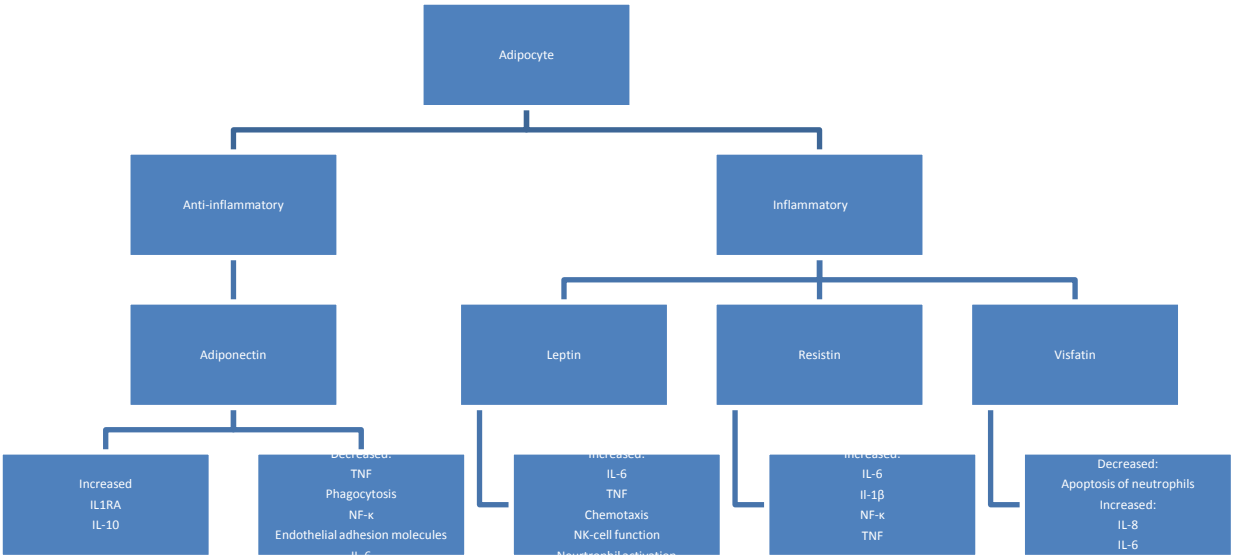

Table 1. Characteristics of study participants by race/ethnicity*

	Overall	Caucasian	Africa American	P Valueł
N	43	21	22	
Age (y)	30.2 (8.6)	28.9 (8.1)	31.3 (8.9)	0.35
Sex				0.89
Male, n (%)	20 (46.5)	10 (47.6)	10 (45.4)	
Female, n (%)	23 (53.5)	11 (52.4)	12 (54.6)	
Body mass index (kg/m^2)	26.6 (4.4)	25.9 (4.3)	27.3 (4.6)	0.27
Waist conference (cm)	89.1 (12.5)	87.5.0 (12.5)	90.6 (12.4)	0.42

* Data are given as mean (standard deviation) unless otherwise specified
ł P value for difference between Caucasians and African Americans by Fisher's exact X^2 test for categorical variables or t test for continues variables.

Table 2. Vascular assessments and serum lipid levels by race/ethnicity*

	Overall	Caucasian	Africa American	P Valueł
N	43	21	22	
% FMD	0.076 ± 0.008	0.073 ± 0.008	0.078 ± 0.013	0.75
Supine systolic BP (mmHg)	116.8 ± 2.1	113.7 ± 1.6	119.7 ± 3.8	0.30
Supine diastolic BP (mmHg)	74.0 ± 1.6	72.2 ± 1.2	75.6 ± 2.8	0.45
Cholesterol (mg/dL)	161.6 ± 3.94	168.9 ± 5.0	154.6 ± 5.8	0.06
Triglyceride (mg/dL)	69.2 ± 5.5	74.6 ± 9.5	64.1 ± 5.7	0.26
LDL (mg/dL)	100.5 ± 4.4	106.4 ± 6.7	94.9 ± 5.6	0.08
HDL (mg/dL)	47.2 ± .2.6	47.6 ± 4.0	46.8 ±3.4	0.63
LDL/HDL ratio	2.61 ± 0.27	2.92 ± 0.49	2.31 ± 0.25	0.12

* Data are given as mean ± standard error
ł P values for difference between Caucasians and African Americans by Proc General Linear Model (GLM) adjusted for age (continuous), body mass index (continuous), and sex.

Abbreviations: BP, blood pressure; FMD, flow mediated dilation; LDL, low density lipoprotein; HDL, high density lipoprotein.

Table 3. Serum obesity and inflammatory biomarkers by race/ethnicity*

	Overall	Caucasian	Africa American	P Valueł
N	43	21	22	
Leptin (ng/mL)	18.05 ± 2.99	19.11 ± 4.77	17.04 ± 3.74	0.13
Adiponectin (µg/mL)	10.03 ± 1.17	12.25 ± 1.81	7.91 ± 1.38	0.09
hsCRP (mg/L)	1.43 ± 0.32	1.51 ± 0.40	1.35 ± 0.51	0.26
IL-1β (pg/mL)	0.87 ± 0.08	0.99 ± 0.14	0.77 ± 0.10	0.22
IL-2 (pg/mL)	13.75 ± 1.86	17.77 ± 3.42	9.91 ± 1.21	0.01
IL-4 (pg/mL)	8.65 ± 0.61	9.76 ± 0.84	7.60 ± 0.83	0.04
IL-5 (pg/mL)	2.76 ± 0.23	2.71 ± 0.24	2.80 ± 0.40	0.85
IL-6 (pg/mL)	12.42 ± 5.24	9.01 ± 1.56	15.68 ± 10.21	0.26
IL-8 (pg/mL)	7.06 ± 0.59	7.22 ± 0.69	6.90 ± 0.96	0.37
IL-10 (pg/mL)	3.91 ± 0.47	4.70 ± 0.75	3.16 ± 0.52	0.055
TNF-α (pg/mL)	7.16 ± 1.48	8.10 ± 1.46	6.26 ± 2.56	0.06
IFN-ɣ (pg/mL)	1.09 ± 0.09	1.27 ± 0.15	0.91 ± 0.09	0.02
GM-CSF (pg/mL)	4.04 ± 0.51	4.75 ± 0.70	3.36 ± 0.74	0.04
IL-6R (ng/mL)	29.98 ± 0.49	31.60 ± 0.54	28.44 ± 0.65	0.005
IL-1RA (pg/mL)	6609 ± 199	7200 ± 262	6044 ± 246	0.002
TNF-RI (pg/mL)	984 ± 54	1109 ± 79	865 ± 65	0.008
TNF-RII (pg/mL)	3550 ± 107	3646 ± 146	3458 ±157	0.39

*Data are given as mean ± standard error
ł P values for difference between Caucasians and African Americans by Proc General Linear Model (GLM) adjusted for age (continuous), body mass index (continuous), and sex.
For CRP, Leptin, IL-2, IL-6, IL-10, TNF-α, and GM-CSF, log-transformed values were used for P value calculation.

Abbreviations: hsCRP, high sensitive C-reactive protein; IL, interleukin; TNF, tumor necrosis factor; IFN, interferon; GM-CSF, granulocyte-macrophage colony-stimulating factor. IL-6R, IL-6 receptor; IL-1RA, IL-1 receptor antagonist, TNF-RI, TNF receptor type I, TNF-RII, TNF receptor type II.

Table 4. Serum obesity and inflammatory biomarkers by race/ethnicity stratified by sex*

	Male				Female			
	Overall	Caucasian	African American	P Valueł	Overall	Caucasian	African American	P Valueł
N	20	10	10		23	11	12	
Leptin (ng/mL)	8.09 ± 1,82	8.47 ± 2.88	7.71 ± 2.38	0.82	26.71 ± 4.69	28.79 ± 7.79	24.80 ± 5.76	0.85
Adiponectin (µg/mL)	7.54 ± 1.22	9.67 ± 1.95	5.42 ± 1.24	0.08	12.20 ± 1.81	14.60 ± 2.87	9.99 ± 2.18	0.21
CRP (mg/L)	1.19 ± 0.23	1.28 ± 0.33	1.10 ± 0.33	0.69	1.64 ± 0.56	1.72 ± 0.71	1.57 ± 0.92	0.69
IL-1β (pg/mL)	0.81 ± 0.10	0.93 ± 0.16	0.69 ± 0.12	0.26	0.94 ± 0.13	1.06 ± 0.23	0.83 ± 0.14	0.40
IL-2 (pg/mL)	14.58 ± 2.72	17.66 ± 5.07	11.50 ± 1.82	0.30	13.03 ± 2.60	17.88 ± 4.87	8.58 ± 1.59	0.02
IL-4 (pg/mL)	8.40 ± 0.85	10.02 ± 1.29	6.78 ± 0.91	0.055	8.87 ± 0.87	9.52 ± 1.16	8.27 ± 1.31	0.49
IL-5 (pg/mL)	2.57 ± 0.29	2.66 ± 0.32	2.48 ± 0.49	0.77	2.92 ± 0.36	2.76 ± 0.37	3.07 ± 0.62	0.68
IL-6 (pg/mL)	18.52 ± 11.18	8.85 ± 2.09	28.19 ± 22.43	0.89	7.12 ± 1.26	9.15 ± 2.39	5.26 ± 0.83	0.14
IL-8 (pg/mL)	5.95 ± 0.64	6.20 ± 0.96	5.71 ± 0.89	0.72	8.02 ± 0.92	8.17 ± 0.95	7.89 ± 1.58	0.88
IL-10 (pg/mL)	3.58 ± 0.51	4.21 ± 0.77	2.95 ± 0.63	0.16	4.20 ± 0.76	5.15 ± 1.28	3.33 ± 0.82	0.17
TNF-α (pg/mL)	8.05 ± 1.55	11.64 ± 2.59	4.46 ± 0.75	0.01	6.38 ± 2.44	4.88 ± 0.70	7.76 ± 4.69	0.71
IFN-ᵞ (pg/mL)	0.87 ± 0.08	0.95 ± 0.12	0.78 ± 0.11	0.30	1.27 ± 0.44	1.55 ± 0.24	1.02 ± 0.14	0.06
GM-CSF (pg/mL)	4.18 ± 0.88	4.44 ± 0.89	3.92 ± 1.56	0.34	3.92 ± 0.60	5.03 ± 1.09	2.89 ± 0.45	0.20
IL-6R (ng/mL)	29.74 ± 0.77	32.17 ± 0.54	27.32 ± 0.95	0.0003	30.19 ± 0.63	31.09 ± 0.91	29.37 ± 0.84	0.18
IL-1RA (pg/mL)	6766 ± 353	7702 ± 348	5831 ± 460	0.005	6471 ± 213	6744 ± 346	6222 ± 249	0.23
TNF-RI (pg/mL)	1030 ± 83	1267 ± 96	792 ± 84	0.002	945 ± 71	965 ± 109	926 ± 97	0.79
TNF-RII (pg/mL)	3699 ± 125	3937 ± 136	3461 ± 186	0.05	3420 ± 167	3381 ± 228	3456 ± 251	0.83

*Data are given as mean ± standard error

ł P values for difference between Caucasians and African Americans by t test. For CRP, Leptin, IL-2, IL-6, IL-10, TNF-α, and GM-CSF, log-transformed values were used for P value calculation.

Abbreviations: hsCRP, high sensitive C-reactive protein; IL, interleukin; TNF, tumor necrosis factor; IFN, interferon; GM-CSF, granulocyte-macrophage colony-stimulating factor. IL-6R, IL-6 receptor; IL-1RA, IL-1 receptor antagonist, TNF-RI, TNF receptor type I, TNF-RII, TNF receptor type II.

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