Role of plasma adiponectin /C-reactive protein ratio in obesity and type 2 diabetes among African Americans.

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Abstract

Background: Obesity is a modifiable risk factor for hypertension and T2D.

Objective(s): We examined relations between fasting plasma adiponectin (ADIP), C-reactive protein (CRP) concentrations and markers of T2D in African Americans (AA).

Methods: Fasting plasma ADIP, CRP, Insulin (IN), HOMA-IR, lipid profiles, body fat percent (%BF), waist circumference (WC), body mass index (BMI) and blood pressure measures were determined in AA women (W: n=77) and men (M: n=34). Participants were classified into: 1) Normal fasting glucose (FG) and Normal %BF; 2) Normal FG and High %BF; and 3) High FG.

Results: Compared to men, women had significantly higher mean ADIP (W: 31.4±2.9 vs. M: 18.0±4.4 ng/L), CRP (W: 3.2±0.3 vs. M: 2.0±0.5 mg/L), %BF (W: 41.2±0.9 vs. M: 27.2±1.3), and BMI (W: 32.3±0.7 vs. M: 29.2±1.1 kg/m2). Women with normal FG and %BF had significantly higher ADIP (64.0±6.0) and lower CRP (1.3±0.6) concentrations than normal FG/ high %BF (ADIP: 37.0±5.0 and CRP: 3.1 ±0.5) and high FG (ADIP: 15.1±4.1 and CRP: 4.0 ± 0.5) groups. Women with high ADIP to CRP ratio had favorable metabolic and anthropometric profiles.

Conclusion: Low ADIP and high CRP are associated with excessive %BF and FG in AA women. ADIP/CRP, may be useful for detecting metabolic dysregulation.

Keywords: Obesity, type 2 diabetes, inflammation.

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Introduction

Obesity, defined as an accumulation of excess body fat[1,2], increases the risk of developing insulin resistance (IR) and type 2 diabetes (T2D)[3]. Since these conditions reflect metabolic dysregulation and likely systemic inflammation, interest in various bio-active proteins has emerged. Two proteins of interest are adiponectin and C reactive protein (CRP), produced by adipose tissue and the liver, respectively[4]. The significant inverse correlation between anti-inflammatory adiponectin and pro-inflammatory CRP reported in certain obese, diabetic and coronary artery disease (CAD) populations[5], underscores the importance of investigating adiponectin and CRP together to elucidate their opposing relationships in obesity and T2D.

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Adipose tissue has traditionally been seen as a storage place for fatty acids; however this notion has been replaced over the last years and adipose tissue has been recognized to play a central role in lipid and glucose metabolism and production of various hormones and cytokines[6]. Adipose tissue is an active endocrine organ that secretes adipocytokines, such as adiponectin. Adiponectin has anti-diabetic and anti-inflammatory properties[7] and appears to be higher in women than men[8-10]. Discovered in the mid-1990s by four different research groups, it is also referred to as Acrp30, AdipoQ, ApM1, and GBP28[11]. Within the general population, high adiponectin levels

have been associated with positive cardiovascular benefits; whereas low values of adiponectin have been linked to a variety of health risks - obesity, metabolic syndrome (MS), IR, T2D and unfavorable lipid profiles[12-15]. Other studies have reported that individuals with CAD and/or T2D have lower plasma adiponectin levels than age- and body mass index- (BMI) matched, non-diabetic individuals without CAD[16]. Little is known about the regulation of adiponectin, especially in African Americans (AA) and most of the factors and mechanisms affecting adiponectin levels are poorly described[17].

CRP is another important systemic marker for inflammation and high CRP levels have also been linked to multiple health risks - obesity, T2D, cardiovascular disease (CVD), and hyperlipidemia[18-20]. Due to the apparent strong associations between CRP and health risks, the American Heart Association and Centers for Disease Control and Prevention evaluated CRP as a risk assessment tool and proposed cut points of <1 mg/L, 1-3 mg/L and >3 mg/L be used to identify those at low, average, and high relative risk, respectively for CVD[21]. Plasma CRP correlates positively with body fat mass, visceral adipose tissue accumulation and plasma insulin[22], and is associated with T2D[23]. Conflicting results have been found with regard to gender differences in CRP. Whereas some studies have reported higher CRP levels in women[24,25], others have found no gender differences[26]. Ethnic differences in CRP concentrations have also been noted: two large cohort studies found that CRP tends to be higher in AA and Hispanic women than Caucasians and Asian women[27,28].

However, some obese individuals are free from obesity-related metabolic complications[29]. The aim of this study was to evaluate associated patterns of plasma adiponectin and high sensitivity CRP (hs-CRP) concentrations as a function of metabolic risk factors - fasting blood glucose (FG), insulin (IN), waist circumference (WC), percent body fat (% BF), mean arterial blood pressure (MAP) and plasma lipids (high density lipoprotein cholesterol/ HDL-C and triglycerides/TG). We hypothesized that, among individuals with increased FG and %BF, combining adiponectin and CRP would provide a valuable index of obesity related inflammatory and metabolic markers. Therefore, we examined mean differences in metabolic characteristics based on the combined measurements of adiponectin and CRP in AA men and women after classifying participants into three metabolic risk groups: (a) normal FG and %BF; (b) normal FG and high %BF; and (c) high FG. In addition we determined whether the plasma adiponectin to CRP ratio level would be a predictive measure of metabolic risk.

Methods

Study population

Participants with complete dataset included 111 AA men (n= 34) and women (n = 77) between 18 to 60 years of age who were recruited between January 2008 and September 2009 through public advertisements and announcements at local churches in the Greater Washington DC area. Participants who were pregnant or taking steroid medications were excluded for distinct hormonal profiles associated with circulating levels of adiponectin. The study was approved by the Institutional Review Board of the Uniformed Services University of the Health Sciences (USUHS), and written informed consent was obtained from all participants.

Procedures

Participants visited the laboratory between 0700 and 0900 AM, wherein after obtaining informed consent, blood pressure (BP) and anthropometric evaluations were obtained. Baseline blood collections were obtained after an overnight fast for determination of glucose, insulin, HDL-C, TG, hs-CRP and adiponectin.

Anthropometric measurements

Body weight was measured with a calibrated balance beam metric scale to the nearest 0.1kg and height was measured with a stadiometer to the nearest 0.1cm. BMI was calculated from height and weight (kg/m2). %BF was estimated by using bioelectric impedance and calculated with the NHANES III prediction formula. WC was measured at the midpoint between the lower rib margin and the iliac crest by using a non-elastic measuring tape. Baseline BP was recorded with a standard BP monitor: measurements were obtained on at least two occasions with the participant in a seated position to ensure accurate assessment. Mean arterial pressure (MAP) was calculated using the formula ((2*Diastolic BP) + (Systolic BP))/3[30].

Physiological and biochemical measurements

Fasting blood glucose concentration was measured with One Touch Ultra monitoring system, hs-CRP analyses were carried out with an Immulite 2000 analyzer (Siemens Medical Solutions Diagnostics, Erlanger, Germany), Insu-

lin was detected using the Human Insulin ELISA kit from Millipore (St.Charles, Missouri, USA), Adiponectin was detected using the Human Adiponectin sandwich immunoassay kit from Meso Scale Discovery (Gaithersburg, MD, USA) and lipid profiles (Total Cholesterol, HDL-C, LDL-C and TG) were determined in the Clinical Laboratory at the National Institutes of Health Department of Laboratory Medicine using an LX-20 analyzer (Beckman, San Diego, CA). Mean values are expressed in mm/L, μU/mL, mg/L, ng/mL and mmol/L respectively. Insulin Resistance was defined by using homeostasis model asessment method of insulin resistance (HOMA-IR) (glucose [in millimoles per liter] x insulin [in microunits per milliliter]/22.5).

Statistical analysis

The frequency and distributions of variables were examined to determine normality of distribution and identify outliers. Distributions of plasma adiponectin and CRP levels were skewed, so natural log transformed values were used to normalize the variables for analyses. Men and women with a %BF ≥ 25.1 and 35.1 respectively, were categorized as high %BF and participants with FG ≥ 6.1 mmL were considered as diabetic. Three groups were then formed based on FG and %BF: 1) low risk – normal FG and %BF; 2) moderate risk – normal FG and high %BF; and 3) high risk - high FG. Covariates, such as age and income, were controlled for in all analyses.

In addition, the ratio of adiponectin (values were multiplied by 1,000 to generate whole numbers greater than 0.1) to CRP was calculated (mg/L). Cut points were made for 2 groups and participants in the lower point of adiponectin to CRP ratio were classified as "high risk", participants in the upper point were classified as "low risk". Multivariate analyses of variance (MANOVA) were used to determine differences in (1) metabolic (FG, IN, HOMA-IR), lipid profiles (TC, TG, LDL-C and HDL-C) and physical variables (BMI, %BF, WC, MAP) as a function of metabolic grouping low and high adiponectin to CRP ratio and (2) variations in plasma adiponectin, CRP and adiponectin to CRP ratio in the three %BF and diabetes status groups. Partial correlations were calculated to find associations between adiponectin and CRP with physical, lipid and metabolic measurements.

The sample size of 111 (69% female) was adequate to detect moderate group differences across two independent groups of different sizes (d=0.6), and across three sized groups (f=0.30). Participants with complete data were included in the present analysis. Results are expressed as mean ± SEM and the statistical significance was set at $p \leq 0.05$. Statistical analyses were performed with IBM SPSS 20.0 for Windows (SPSS Inc., Chicago, Ill., USA).

Results

Compared to men, women had higher plasma hs-CRP (Women: 3.2 ± 0.3 mg/L, Men: 2.0 ± 0.5 mg/L; $p \leq 0.05$), adiponectin (Women: 31.4 ± 2.9 ng/mL, Men: 18.0 ± 4.4 ng/mL; $p \leq 0.05$), %BF (Women: 41.2 ± 0.9, Men: 27.2 ± 1.3; $p \leq 0.001$) and BMI (Women: 32.3 ± 0.7,

Table 1: Metabolic and physical characteristics by gender (Mean ± S.E.M)

Variables	Women (n=77)	Men (n=34)
CRP (mg/L)*	3.2 ± 0.3	2.0 ± 0.5
Adiponectin (ng/mL)**	31.4 ± 2.9	18.0 ± 4.4
[1]Adiponectin/CRP ratio	43.2 ± 7.5	28.0 ± 11.3
Total Cholesterol (mmol/L)	4.1 ± 0.1	4.0 ± 0.1
Triglycerides (mmol/L)	1.0 ± 0.1	1.2 ± 0.1
LDL-C (mmol/L)	2.4 ± 0.1	2.3 ± 0.1
HDL-C (mmol/L)	1.3 ± 0.04	1.2 ± 0.06
Fasting Glucose (mmol/L)	6.2 ± 0.2	6.3 ± 0.2
Insulin (μU/mL)	7.5 ± 0.9	7.4 ± 1.3
HOMA-IR	2.2 ± 0.3	2.2 ± 0.4
Waist Circumference (cm)	99.0 ± 2.0	98.5 ± 3.0
Percent Body Fat***	41.2 ± 0.9	27.2 ± 1.3
Body Mass Index (kg/m^2)*	32.3 ± 0.7	29.2 ± 1.1
MAP (mm Hg)	99.0 ± 2.0	101.0 ± 2.3

Note: Mean Differences significant at *p≤ 0.05, **p ≤0.01, ***p≤0.001 (controlled for age and income;[1]ratio of adiponectin (values multiplied by 1000 to generate whole numbers) to CRP.
Abbreviations: C reactive protein (CRP); Low-Density Lipoprotein Cholesterol (LDL-C); High-Density Lipoprotein Cholesterol (HDL-C); Homeostasis Model Assessment Method of Insulin Resistance (HOMA-IR); Mean Arterial Pressure (MAP).

Men: 29.2 ± 1.1; p ≤ 0.05), as shown in Table 1.

Table 2 presents correlation coefficients for plasma adiponectin and CRP with physical (BMI, WC, MAP and %BF), metabolic and lipid (FG, IN, HOMA-IR, TC, TG, LDL-C and HDL-C) variables. A significant negative correlation was observed between plasma adiponectin and CRP in AA men (r = -0.39, p ≤ 0.05) and women (r = -0.32, p ≤ 0.01). Adiponectin was significantly and negatively associated with BMI and WC in both men and women, whereas in women only, adiponectin was also associated with %BF, IN, FG and HOMA-IR. In men, there was a significant negative association between CRP and HDL-C; a positive association between CRP and BMI in both men and women and with WC, %BF, FG, IN and HOMA-IR, in women only.

Table 2: Partial correlations between adiponectin, CRP, physical and metabolic variables by gender (Women: n = 77; Men: n = 34)

Variables	Adiponectin		CRP	
	Women	Men	Women	Men
Adiponectin (mg/L)	-	-	-0.32**	-0.34*
CRP (mg/L)	-0.32**	-0.39*	-	-
BMI (kg/m^2)	-0.23*	-0.40*	0.51***	0.45**
WC (cm)	-0.30**	-0.34*	0.57***	0.32
MAP (mm Hg)	0.13	-0.13	0.16	0.002
Body Fat (%)	-0.24*	-0.26	0.50***	0.33
FG (mmol/L)	-0.34**	-0.05	0.30**	-0.10
IN (μU/mL)	-0.33**	-0.11	0.30*	0.17
HOMA-IR	-0.33**	-0.12	0.30**	0.15
TC (mmol/L)	-0.10	-0.15	0.12	0.04
TG (mmol/L)	-0.22	-0.23	0.16	0.13
LDL-C (mmol/L)	-0.13	-0.15	0.16	0.17
HDL-C (mmol/L)	0.16	0.17	-0.11	-0.36*

Note: Significance of correlation coefficients shown at *p≤ 0.05, **p ≤0.01, ***p≤0.001 (controlled for age and income).
Abbreviations: C reactive protein (CRP); Body Mass Index (BMI); Waist Circumference (WC); Mean Arterial Pressure (MAP); Fasting Glucose (FG); Insulin (IN); Homeostasis Model Assessment of Insulin Resistance (HOMA-IR); Total Cholesterol (TC); Triglycerides (TG); Low-Density Lipoprotein Cholesterol (LDL-C); High-Density Lipoprotein Cholesterol (HDL-C).

Table 3 shows metabolic and physical baseline differences based on low and high adiponectin to CRP ratio. AA women with a high adiponectin to CRP ratio had significantly lower FG, IN, HOMA-IR, WC, %BF and BMI while for men, only HDL-C, BMI and %BF were signifi-

Table 3: Metabolic and physical characteristic based on low and high a diponectin to CRP ratio (Mean ± S.E.M)

Variables	Adiponectin/CRP ratio WOMEN		Adiponectin/CRP ratio MEN	
	Low (n= 39)	High (n=38)	Low (n=17)	High (n=17)
TC (mmol/L)	4.2 ± 0.1	4.0 ± 0.1	4.1 ± 0.2	4.1 ± 0.2
LDL-C (mmol/L)	2.4 ± 0.1	2.3 ± 0.1	2.4 ± 0.1	2.2 ± 0.2
TG (mmol/L)	1.1 ± 0.1	1.0 ± 0.1	1.4 ± 0.1	1.0 ± 0.1
HDL-C (mmol/L)	1.3 ± 0.1	1.3 ± 0.1	1.1 ± 0.1*	1.3 ± 0.1
FG (mmol/L)	6.4 ± 0.1**	6.0 ± 0.2	7.0 ± 0.5	6.2 ± 0.5
IN (μU/mL)	10.0 ± 1.0**	5.0 ± 1.0		
HOMA-IR	3.0 ± 0.3**	1.4 ± 0.3	3.0 ± 0.7	1.4 ± 0.7
WC (cm)	104.1 ± 2.6**	92.1 ± 3.0	104.1 ± 3.7	94.1 ± 4.0
BF (%)	44.0 ± 1.2**	39.0 ± 1.3	30.0 ± 1.3*	25.2 ± 1.3
BMI (kg/m2)	34.4 ± 1.1***	30.1 ± 1.1	31.2 ± 1.2*	27.3 ± 1.1
MAP (mm Hg)	99 ± 2.0	97 ± 2.3	101 ± 3.3	102 ± 3.3

Note: Mean Differences significant at *p≤ 0.05, **p ≤0.01, ***p≤0.001; (controlled for age and income; participants who were in the lower 50 percentile of adiponectin to CRP ratio were classified as "low", participants in the upper 50 percentile were classified as "high").

Abbreviations: Total Cholesterol (TC); Low-Density Lipoprotein Cholesterol (LDL-C); Triglycerides (TG); High-Density Lipoprotein Cholesterol (HDL-C); Fasting Glucose (FG); Insulin (IN); Homeostasis Model Assessment of Insulin Resistance (HOMA- IR); Waist Circumference (WC); Body Mass Index (BMI); Mean Arterial Pressure (MAP).

cantly different between the two ratio groups.

Figure 1 presents mean plasma adiponectin, CRP and adiponectin to CRP ratio by the three metabolic groupings and gender. Women with normal FG/%BF had significantly higher adiponectin (64±6.0 ng/mL) and lower CRP (1.3±0.6 mg/L) concentrations than women with normal FG and high %BF (adiponectin: 37.0 ±5.0 ng/mL and CRP: 3.1±0.5 mg/L) and high FG (adiponectin: 15.1 ± 4.1 ng/mL and CRP: 4.0 ± 0.5mg/mL). Additionally, adiponectin to CRP ratio differed significantly in all three groups among women. This pattern did not hold in AA men.

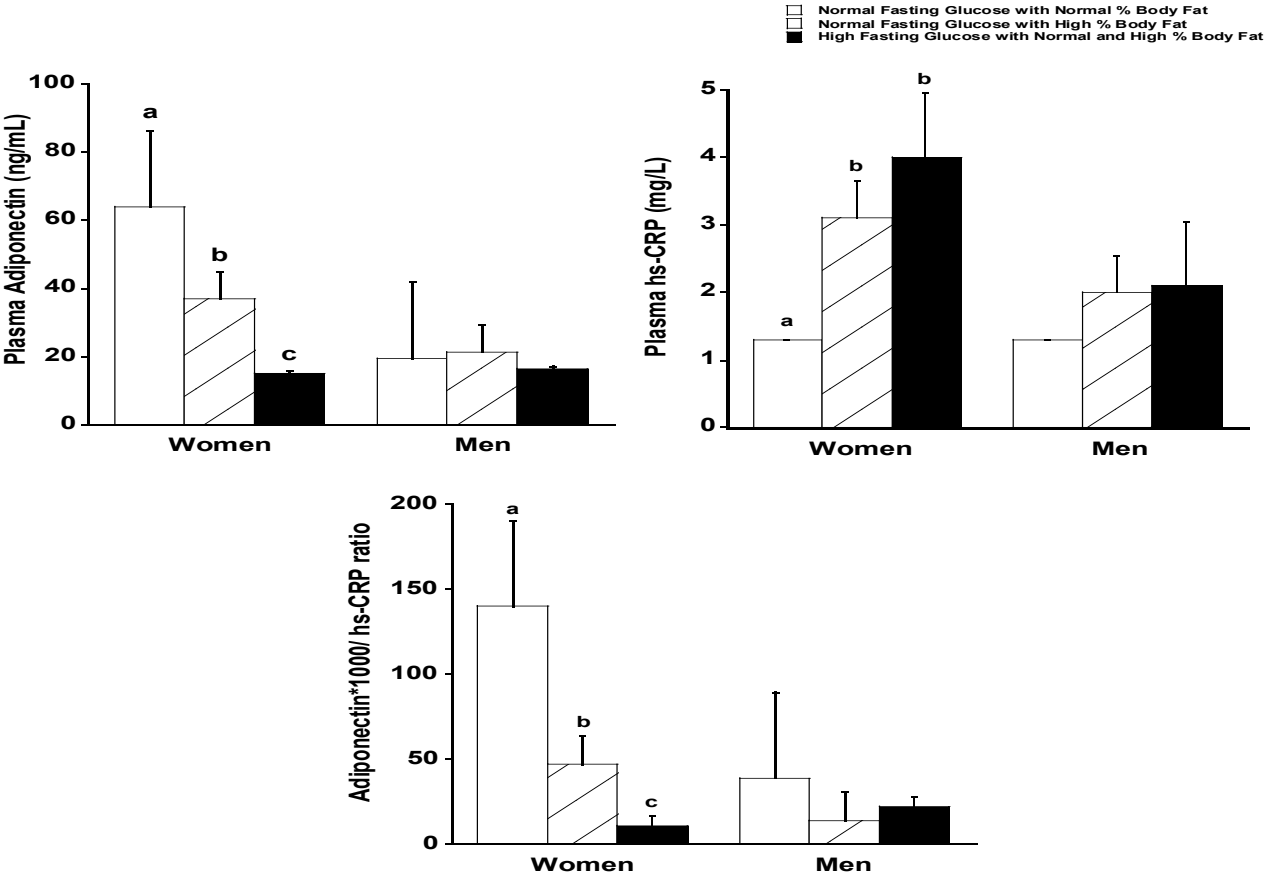

Figure 1: Plasma adiponectin, CRP, and the adiponectin to CRP ratio based on normal %body fat and fasting glucose (Women = 23; Men = 16), high %body fat and normal fasting glucose (Women = 30; Men = 12) and normal/high % body fat/high fasting glucose (Women = 43; Men = 21) (Mean ± S.E.M)

Note: Means with different superscript letters differ significantly; p≤ 0.05 (controlled for age and income; ratio of adiponectin to CRP values were multiplied by 1000 to generate whole numbers). Abbreviations: CRP: C-Reactive Protein).

Discussion

Excessive body fat is a major risk for cardiovascular disease and increases the risk of hypertension, dyslipidemia, hyperglycemia and low-grade inflammation process. Two proteins that are associated with T2D and obesity are adiponectin and CRP. Adiponectin is exclusively produced by adipocytes, circulates in plasma, and is reduced in obesity, IR, MS and T2D. Adiponectin helps to regulate the release of various inflammatory and anti-inflammatory cytokines[13,31]. Whereas CRP released from the liver in response to the inflammatory cytokines - IL-1 beta, IL-6 and TNF-alpha is a risk factor for cardiovascular events and is related to an increased risk of incident T2D. Although CRP and adiponectin were negatively related, results from the present study strongly suggests that AA women with low adiponectin and high CRP are likely to have excessive body fat and glucose dysregulation as compared to AA women with high adiponectin and low CRP values. In contrast, women who are obese, but not pre-diabetic, are likely to have moderately high adiponectin and CRP values. A predictive cut-off for adiponectin could be developed, but an adiponectin/CRP ratio may

preclude the need for such a cut-off.

Previous studies have shown that circulating CRP is a predictor of CVD[32] whereas adiponectin levels are reflective of IR, central obesity and intra-abdominal fat accumulation[16,33,34]. In the present study, adiponectin was negatively correlated with many markers (BMI, WC, %BF, and FG), whereas CRP was positively correlated with various metabolic markers (BMI, WC, %BF, IN, FG and HOMA-IR) in AA women. Although CRP and adiponectin were negatively related, the strength of the relationship was low; combining the two variables may provide more valuable information regarding obesity and diabetes than any of the individual variables. Interestingly, the observed trends were not seen in AA men.

Adiponectin and CRP are independent risk factors of CVD, together serve a synergistic role in metabolic regulation in the general population and T2D subjects[35-37]. We found that AA women with high adiponectin and low CRP levels, which translated into a high ratio, had significantly lower FG, IN, HOMA-IR, WC, %BF and BMI relative to those with a low ratio. A combined measurement of these markers may be more useful for detecting persons at high risk for cardiovascular disease and diabetes, than one of the measure alone.

Although obesity is a risk factor for insulin resistance, CVD and T2DM, not every obese individual suffers the same metabolic dysregulation. In the 1980s, a subgroup of metabolically normal, but obese, individuals with relatively high insulin sensitivity and a favorable metabolic profile was reported by several investigators[38]. A unique subset of obese individuals appears to be protected from developing the metabolic disturbances typically associated with obesity. These individuals, despite being obese display normal to high insulin sensitivity and favorable cardiovascular risk profiles[39-43]. Thus, it is important to characterize differences between these groups to uncover additional mechanisms connecting obesity and health risk. In our study, we examined differences in adiponectin and CRP and the adiponectin to CRP ratio in AA men and women with normal %BF/FG, high %BF/normal FG and normal and high %BF with high FG. Whereas no differences were noted between the men by metabolic group assignment, plasma adiponectin was consistently lower and CRP higher in women in the high FG group compared to women in the normal %BF/FG and in the high %BF/normal FG group. The high FG also had a significantly lower adiponectin to CRP ratio relative to the other metabolic groups of women. Our findings are also consistent with epidemiological studies showing that circulating levels of adiponectin are lower in diabetic than in healthy individuals[44,45]. Additionally, studies have reported that heavier individuals had greater health benefit and lower health risks from high levels of adiponectin than their lean counterparts[46,47]. Whether a combined measure of these two markers, such as adiponectin/CRP ratio, would be useful for detecting and monitoring metabolic and low-grade inflammation health risk in AA women remains to be fully understood.

Gender differences in adiponectin and CRP levels have previously been reported[23,48,49], and our study provides further evidence of these gender differences because AA women had significantly higher adiponectin and CRP levels than AA men. Additionally, we found a significant negative association between plasma adiponectin and CRP in both genders.

Limitations

We had data on fewer men than women, and this may have limited our findings among men. The present study examined only AA and it would be interesting to examine differences across other ethnic overweight/obese and diabetic/ non diabetic groups by gender as well. Longitudinal research with more participants will be necessary to determine the independent and interactive relationships between adiponectin and hs-CRP, and the health outcomes they reflect.

Conclusion

A statistically significant negative association was observed between plasma adiponectin and CRP in both AA men and women; AA women had higher adiponectin and CRP levels compared to AA men. Overall, AA women with high fasting glucose and HOMA -IR had lower concentrations of adiponectin and higher CRP levels than AA women with normal glucose. Measures of obesity and metabolic dysregulation are more strongly related to CRP and adiponectin in AA women than in AA men. Finally, the ratio of circulating levels of adiponectin to CRP was examined and found to discriminate between AA women who were diabetic versus those who were not, regardless of obesity status, which suggests that adiponectin may have a protective effect against obesity related metabolic derangements in AA women. Prospective studies will be

needed to confirm this finding.

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Conflict of interest and disclaimer

The authors have no conflict of interests in the present study. The views expressed are those of the authors and do not reflect the official policy position of the USUHS, Department of the Army, Department of the Navy, Department of Air Force, the United States Department of Defense or the United States Government.

Author contributions

Preetha Anna Abraham: drafted and wrote the present manuscript, contributed to the conception and design of research, acquisition of data, prepared figures, performed experiments, and conducted statistical analysis; Selasi Attipoe: assisted with performing experiments, acquisition of data, and manuscript preparation; Josh Kazman: assisted with statistical analyses and interpretation of results; Stacey Zeno: supervision of study execution, acquisition of data, and assisted with manuscript preparation; Merrily Poth and Patricia Deuster: acquired funding for the research, supervision of study execution, contributed to the study design, edited and approved the final version of the manuscript.

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