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Oxidative stress, oxidative balance score, and hypertension among a racially diverse population

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Abstract

Hypertension is a risk factor for several vascular diseases. Evidence suggests that oxidative stress (OS) plays a significant role in its pathophysiology. Human studies have shown inconsistent results, varying based on the OS biomarker and study population. In a racially diverse population, examine the association between: (1) blood pressure or hypertension and four markers of OS and (2) blood pressure or hypertension and oxidative balance score (OBS). Using data (n = 317) from the cross-sectional study on race, stress, and hypertension, an OBS was constructed from various measures of pro-oxidant and antioxidant exposures. OS was assessed by four biomarkers: fluorescence oxidative products, F_2-isoprostanes, mitochondrial DNA copy number, and gamma tocopherol. Multivariate linear and logistic regression analyses were used to estimate the associations of interest. None of the adjusted associations between hypertension and OS markers was statistically significant. OBS was inversely associated with hypertension after adjusting for study covariates. Persons with higher OBS have lower odds of having hypertension; however, the evidence on the relationship between OS markers and blood pressure remains unconvincing.

Keywords

Antioxidants; blood pressure

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Introduction

Oxidative stress (OS), defined as an imbalance between pro-oxidants and antioxidants in favor of the former,[1] has been identified as a major player in the pathogenesis of hypertension.[2,3] OS is generally the result of overproduction of reactive oxygen and nitrogen species, which in turn damage essential biomolecules such as proteins, lipids, and DNA leading to several human illnesses.[4,5] Hypertension has been associated with higher levels of OS, although it remains unclear whether increased OS is a cause or a consequence of hypertension.[6] Most of the evidence supporting the relationship between OS and hypertension comes from basic science and animal studies.[7,8] In humans, however, the results have not been entirely consistent and efficacy of antioxidant supplementation in reducing blood pressure has not been shown in large clinical trials.[9,10]

OS cannot be directly observed in vivo because of the short lifespan of reactive oxygen and nitrogen species; however, it can be evaluated in humans using biomarkers.[11] Although some biomarkers of OS are nonspecific, others measure a particular biological or chemical aspect of the process.[12,13] In humans, the results on the association between OS and hypertension have mostly been driven by the type of OS biomarker and population being studied.[14] One of the goals of the present study was therefore to estimate the association between OS and hypertension in a racially and ethnically diverse population using four biomarkers of OS: F_2-isoprotanes (F_2-isoP)—a specific marker of lipid peroxidation[15]; fluorescent oxidative products (FOP)—a nonspecific marker that measures a mixture of analytes resulting from reactions of reactive oxygen species with lipids, proteins, and/or DNA[16]; the number of copies of mitochondrial DNA (MtDNA)—a general marker of cumulative cellular damage[17]; and gamma tocopherol (γ-Toc)—a marker of metabolic response to OS.[18]

One potential reason for the inconsistencies in the relationship between hypertension and OS-related exposures (e.g., antioxidant intake) in humans may be the complexity of the processes through which diet, lifestyle, and other factors impact blood pressure. Previous studies have proposed oxidative balance score (OBS), a measure of the status of pro-oxidants and antioxidants, to be a more accurate representation of the overall OS-related exposures in an individual.[19,20] The present study therefore sought to build on and expand on the existing literature. The specific objectives of the present study were to examine: (1) the relationship between hypertension and each of four biomarkers of OS and (2) the association between hypertension and OBS.

Materials and Methods

Study Population

We used cross-sectional data from a previously conducted study on race, stress, and hypertension. The study was designed to assess the differences in dietary, lifestyle, and psychosocial exposures in relation to blood pressure in a racially and ethnically diverse population. The methods of the study have been described in detail elsewhere.[19] Briefly, the study included individuals aged 25–74 years who self-identified as Non-Hispanic Whites (NHW), African Americans (AA) or West African Immigrants (WAI) and who were

residents of Georgia. NHW and AA subjects were selected from among 800 participants in a previously completed feasibility phase of the Georgia Cohort Study. The WAI subjects were recruited de novo using previously established ties with Atlanta churches that included large proportions of WAI. The sample of Georgia Cohort Study participants was selected after the completion of the WAI recruitment and frequency matched to WAI participants on age and sex. There were 335 individuals who met the initial study inclusion criteria. Of this, 18 participants were excluded from the analyses: 7 had no value for hypertension, and 11 were missing values for all four biomarkers of OS. All methods were reviewed and approved by the Institutional Review Boards of the Emory University and the Georgia State University.

Questionnaire Data

The study-specific questionnaire provided data on demographic characteristics (age, sex, race or origin, and education), medical history (hypertension and use of medications), and lifestyle (physical activity and smoking) for all participants. Blood pressure and anthropometric measures (height and weight) were also taken during data collection sessions. Self-administered questionnaires were returned during the data collection session. We used a previously validated tool for measuring physical activity.[21] The reported and measured body mass index (BMI) were highly correlated ($r = 0.91$).

Blood Samples

All participants provided blood samples that were drawn into five 10-mL Vacutainer tubes (two sodium heparin tubes, one ethylenediaminetetraacetic acid (EDTA) tube, and two red top tubes for serum collection) and immediately plunged into ice and protected from direct light. Plasma, serum, and buffy coat specimens were separated within 4–8 hours by centrifugation under refrigeration, aliquoted, frozen, and stored at −80°C. The aliquots were then shipped overnight on dry ice for molecular analysis by the Molecular Epidemiology and Biomarker Research Laboratory at the University of Minnesota, Minneapolis, MN.

Laboratory Analysis

Plasma lycopene, α-carotene, β-carotene, β-cryptoxan-thin, zeaxanthin, lutein, α-tocopherol, and γ-Toc were measured by a high-performance liquid chromatography assay using previously described methods.[22,23] Serum ferritin was measured by an antibody-based method using Roche 911 analyzer.

Gas chromatography-mass spectrometry,[24] a gold standard for the measurement of F_2-isoP, was used to measure plasma-free F_2-isoP. The F_2-isoP was extracted from the plasma sample with deuterium (4)-labeled 8-iso-prostaglandin F_2 alpha as an internal standard.

The measurement of FOP was performed using a modified method from Shimasaki's which has been previously described.[25] A mixed solution was centrifuged for 10 minutes at 3000 rpm, 1 mL of supernatant was added to cuvettes for spectrofluorometric readings, and a relative fluorescence intensity unit per milliliter of plasma was estimated using the spectrofluorometer.[25] Calibration was performed using standard quinine diluted in 0.1 NH_2SO_4.

The copy number of MtDNA was determined using real-time quantitative polymerase chain reaction described by Shen et al.[26] Two primers were used: one for MtDNA and the other for nuclear DNA. The ratio of MtDNA and nuclear DNA was determined using serially diluted genomic sample DNA of a healthy referent.[26]

Oxidative Balance Score

The OBS was estimated using a priori selected 13 pro-oxidant and antioxidant components according to our previous study[19] and those of others[27,28] as listed in Table 1. The score combined plasma micronutrient measurements and lifestyle behaviors. The plasma level of pro-oxidants and antioxidants was divided into sex and race- or origin-specific tertiles. The number of minutes of physical activity per week was also divided into tertiles. For antioxidants (α-carotene, β-carotene, β-cryptoxanthin, zeaxanthin, lutein, and α–tocopherol) and physical activity, the first to third tertiles were assigned scores of 0–2. For pro-oxidants (ferritin), the first to third tertile were assigned a score of 2–0, respectively. To maintain scoring consistency, we assigned scores of 0–2 to the other categorical OBS components. We assigned a score of 0–2 for obese (BMI ≥30 kg/ m^2), overweight (BMI = 25–29.99 kg/m^2), and normal weight (BMI <25 kg/m^2), respectively. For smoking or alcohol use: never smokers or never drinkers received a score of two; former smokers and former drinkers or those with missing information received a score of one; and current smokers and current drinkers received a score of zero. For nonsteroidal anti-inflammatory drugs (NSAIDs) and aspirin, zero points were assigned to participants who reported no regular use of these medications, one point to those who did not report usage or were missing information, and two points to those who reported regular use. Regular users for both aspirin and NSAID were defined as individuals who were taking these medications at least once every week. The points assigned to each component were summed up to represent the overall OBS. OBS was categorized into three approximately equal intervals; 3–10, 11–17, and 18–25 representing low, medium, and high OBS, respectively. OBS was also used in a separate analysis as a continuous variable.

Blood Pressure and Hypertension

Trained and certified staff took the blood pressure measures. After participants had rested for about 5 minutes seated, three blood pressure measures were taken with at least a minute interval using mercury sphygmomanometry and appropriately sized arm cuffs. The mean of the three blood pressure measures was estimated and used in this study. Systolic and diastolic blood pressure (SBP and DBP) measures were expressed as separate continuous variables. Individuals were considered hypertensive if they met any of the following conditions: (1) ever been told by a health care professional that he or she has hypertension, (2) self-reported antihypertensive medication use, (3) had SBP equal or greater than 140 mmHg, and (4) had DBP equal or greater than 90 mmHg.

Statistical Analysis

The F_2-isoP, FOP, MtDNA, and γ-Toc were each dichotomized into a ‘‘low’’ and ‘‘high’’ using their respective sex and race- or origin-specific median as the cutoff. SBP and DBP

were modeled as continuous variables. Hypertension was dichotomized (hypertensive and normotensive). OBS was used as both a continuous and a three-level categorical variable.

The first series of statistical analyses examined the association between SBP, DBP, and each of the OS markers and OBS as continuous variables in linear regression models. In the second set of analyses, we examined the association of hypertension with OBS and with each biomarker of OS, using categorical definitions of the outcome. The odds ratios (OR) for the continuous OS variables in the logistic regression equation was each scaled to their respective one standard deviation. For OS markers, each linear and logistic regression model adjusted for race or origin, age, sex, education, smoking, aspirin use, and BMI. For analyses involving OBS, we did not control for smoking, aspirin use, or BMI because they were included in the OBS scoring.

All analyses were performed using pairwise deletion method as the default (method 1). To estimate the effect of missing data, a sensitivity analysis was performed by imputing the missing values using the multiple imputation method available in SAS. All models were assessed for collinearity among independent variables and goodness of fit. All estimated measures of association were accompanied by 95% confidence intervals (CIs). Statistical significance was determined at two-sided *P*-value of <.05. All analyses were performed in SAS statistical software version 9.3.[29]

Results

The study population included 100 WAI (32.5%), 121 NHW (39.3%), and 87 AA (28.3%) participants. Approximately 33% of the study participants were hypertensive. Hypertension was more common in AA (45.2%) than in NHW (33.1%) and WAI (24.0%) participants. Varying number of participants had a measure for each of the four biomarkers of OS: F_2-isoP (n = 221), FOP (n = 266), MtDNA (n = 173), and γ-Toc (n = 278).

Among the participants, most (60.3%) were females and more than a third had a college degree (41.9%, Table 2). About 32% were current alcohol users, and 5% were current cigarette smokers. Individuals with hypertension were older and more likely to use aspirin and NSAID regularly. As expected, individuals with hypertension had significantly higher BMI compared with their normotensive counterparts (Table 2). Interindividual variability for OS markers was greatest for FOP (range 0.01–0.21 expressed as average standard reference adjusted) and F_2-isoP (range 14.5–280.1 pg/mL): these two biomarkers showed approximately 20-fold difference between the lowest and the highest values. Other OS biomarkers and OBS did not vary as much within the study population: the ranges for the values were 1.22–5.57 expressed as relative copy numbers for MtDNA, 0.06–0.56 mg/dL for γ-Toc, and 4.0–24.0 for OBS. OBS was inversely but not statistically significantly correlated with F_2-isoP ($r = -0.18$), MtDNA ($r = -0.08$), and γ-Toc ($r = -0.04$). By contrast, correlation between OBS and FOP was positive (r = 0.30) and statistically significant (Table 3).

In the linear regression models evaluating the relationship between blood pressure and each of the OS markers and OBS, increasing levels of γ-Toc were associated with increasing

levels of SBP (β = 22.27; P = .0150) and DBP (β = 14.76; P = .0120) in the crude analyses, but the results were attenuated and were no longer statistically significant after adjusting for study covariates. MtDNA copy number was also inversely associated with DBP (β = −2.32; P = .0123) in the crude but not in the adjusted model. The other OS markers and OBS were not associated with blood pressure in the crude or the adjusted models. The sensitivity analyses were consistent with the original results.

In the logistic regression, the associations of hypertension with the OS biomarkers were in the hypothesized direction, but none of the results were statistically significant after controlling for covariates. Results from the sensitivity analyses did not substantially differ from the original results.

There was a statistically significant association between OBS and hypertension after controlling for race or origin, age, sex, and education. The adjusted OR for middle and higher categories of OBS versus lower category (reference) was 0.30 (95% CI, 0.13–0.72) and 0.17 (95% CI, 0.03–0.95), respectively. For the continuous OBS, the adjusted OR was 0.87 (95% CI, 0.79–0.96). In the sensitivity analyses, the results for the continuous OBS were similar to the original analyses, but the associations with categorized OBS were substantially attenuated (Table 4).

Discussion

Endothelial dysfunction, defined as a shift in endothelium actions toward reduced vasodilation, proinflammatory and prothrombotic state, has been associated with the pathophysiology of hypertension.[30] Although the underlying mechanism is complex and multifactorial, the current evidence indicates that OS may be a key factor in this process.[31] In the present cross-sectional study, we examined the relationship between high blood pressure and OS and OBS, hypothesizing that higher level of OS and lower levels of OBS would be associated with high blood pressure or hypertension.

The findings from the final models did not support our hypothesis that increasing levels of OS markers would be associated with high blood pressure, although we found associations to be in the hypothesized direction. This null finding is consistent with other clinical studies that reported nonsignificant difference in OS levels among individuals with and without hypertension.[32,33]

The observed association between OBS and high blood pressure or hypertension supported our second hypothesis that higher OBS levels would be inversely related to high blood pressure. This finding is consistent with other studies that also noted an inverse relationship between OBS and poor health including risk of prostate cancer[34] and colorectal adenoma.[20] Some previous studies found an inverse association between some of the OBS components and blood pressure.[35–37] For example, Li and Xu[38] recently concluded from a meta-analysis that lycopene supplementation reduces systolic blood pressure. Chen et al. [39] also found lower levels of both α- and β-carotenes in persons with hypertension.

The use of dietary antioxidants to reduce blood pressure is plausible because these compounds have been shown to reduce the bioavailability of reactive oxygen species,

increase production of nitric oxide (NO), downregulate nicotinamide adenine dinucleotide phosphate oxidase, and upregulate endothelial NO synthase.[2,40] Higher production and bioavailability of NO in the endothelial cells are important for vascular relaxation.[41] Despite compelling evidence from experimental biology studies, the findings from clinical studies of the effect of antioxidant supplementation for blood pressure reductions have not produced the desired results.[10,42] The possible reasons for the discrepancy in the use of antioxidants to treat conditions related to OS have been articulated: the type of antioxidants used, patient cohorts, and the trial design.[2] Another possible reason is that antioxidants in diets are mixed and work as continuous chain, whereas supplementations are usually a couple of specific antioxidants and therefore may lack this antioxidant chain. Also, it has been found that if an antioxidant is not restored by the next in the chain after scavenging reactive oxygen species, it begins to act as a pro-oxidant.[3] The evidence therefore suggests that biochemical interactions exist among antioxidants which may be lacking in supplements due to the use of one or two individual antioxidants.[3,43]

Given the inconsistent relationship between OS markers and high blood pressure or hypertension and the inconclusive association between individual antioxidants and high blood pressure or hypertension from previous studies, the use of OBS seems promising, as it represents the overall patterns of pro-oxidant and antioxidant exposures.

An important methodological feature of the present study is the use of a racially and ethnically diverse population. This allowed for assessing multiple biomarkers of OS and their relation to each other and to hypertension in US born whites and blacks and in West Africans. In addition, the use of plasma levels of micronutrients in this study may accurately represent current intake and availability of pro-oxidants and antioxidants compared with food frequency questionnaire-derived measures.[44] The major limitation of this study is the missing information on several variables used in the analyses. Although sensitivity analyses did not affect the overall conclusions, some of the results changed after imputation of missing data.

Conclusion

The presented results suggest that higher OBS may be inversely associated with hypertension, a finding that is consistent with several previous studies. By contrast after controlling for confounders, markers of OS were not associated with blood pressure or hypertension. The discrepancy between relatively consistent associations observed for pro-oxidant and antioxidant exposures and largely null results for markers of OS indicates that OS-related lifestyle and dietary factors may act through other mechanisms. The observed results need to be confirmed in independently conducted, preferably longitudinal, studies. If these findings are indeed confirmed, the mechanisms by which OBS may influence the risk of hypertension need to be explored further.

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Table 1

OBS assignment

Component	Score Assignment
Plasma zeaxanthin	0 = low (first tertile), 1 = medium (second tertile), 2 = high (third tertile)
Plasma cryptoxanthin	0 = low (first tertile), 1 = medium (second tertile), 2 = high (third tertile)
Plasma lycopene	0 = low (first tertile), 1 = medium (second tertile), 2 = high (third tertile)
Plasma *α*-carotene	0 = low (first tertile), 1 = medium (second tertile), 2 = high (third tertile)
Plasma *β*-carotene	0 = low (first tertile), 1 = medium (second tertile), 2 = high (third tertile)
Plasma *α*-tocopherol	0 = low (first tertile), 1 = medium (second tertile), 2 = high (third tertile)
Serum ferritin	2 = low (first tertile), 1 = medium (second tertile), 0 = high (third tertile)
Physical activity	0 = low (first tertile), 1 = medium (second tertile), 2 = high (third tertile)
Alcohol use	0 = current drinker, 1 = former drinker/missing, 2 = never drinker
Smoking	0 = current smoker, 1 = former smoker/missing, 2 = never smoked
Aspirin use	0 = no regular user, 1 = unknown/missing, 2 = regular user
NSAID use	0 = no regular user, 1 = unknown/missing, 2 = regular user
Weight status	0 = obese, 1 = overweight, 2 = normal weight

BMI, body mass index; NSAIDs, nonsteroidal anti-inflammatory drugs; OBS, oxidative balance score.

Normal weight = BMI <25 kg/m^2, overweight = BMI between 25.0 and 29.9 kg/m^2, and obese = BMI ≥30 kg/m^2.

Table 2

Distribution of main study variables

Demographic Characteristics	Overall (n = 317)	Hypertensive and Normotensive Compared		
		Hypertensive (n = 106)	Normotensive (n = 211)	*P*-value
Age	47.1 (11.9)	54.2 (10.6)	43.5 (10.9)	<.001
Female (%)	60.3	64.2	58.3	.3206
Race				
WAI	32.5	23.1	37.3	.0064
NHW	39.3	38.5	39.7	
AA	28.3	38.5	23.0	
Education				
Less than high school	6.8	3.9	8.3	.0495
High school grad	16.1	23.1	12.6	
Some college	35.2	36.5	34.5	
College grad	41.9	36.5	44.7	
OBS measures				
Current alcohol user (%)	32.2	29.3	33.7	.2065
Current smoking (%)	5.0	5.1	5.0	.0856
Obese (%)	44.3	68.9	31.7	<.001
Regular aspirin user (%)	23.3	45.6	12.9	<.001
Regular NSAID user (%)	26.6	32.5	23.8	.1545
Plasma zeaxanthin, ug/dL	20.9 (10.5)	22.6 (11.4)	20.1 (10.0)	.0572
Plasma cryptoxanthin, ug/dL	7.7 (9.1)	8.5 (14.4)	7.4 (4.8)	.3164
Plasma lycopene, ug/dL	45.3 (24.9)	38.7 (18.6)	48.4 (27.0)	.0021
Plasma α-carotene, ug/dL	11 (15.1)	8.6 (13.2)	12.2 (15.9)	.0604
Plasma β-carotene, ug/dL	22.5 (23)	19.2 (18.9)	24.1 (24.6)	.0901
Plasma α-tocopherol, ug/dL	0.96 (0.28)	1.0 (0.3)	0.9 (0.3)	.0012
Serum ferritin, ug/dL	128.1 (226.5)	141.0 (135.2)	121.8 (259.9)	.5009
OBS score	12.2 (3.8)	12.0 (4.2)	12.4 (3.6)	.4407
Biomarkers				
γ-Toc (mg/dL)	0.2 (0.09)	0.22 (0.09)	0.19 (0.09)	.0206
F_2-isoP (pg/mL)	56.6 (34.87)	63.5 (43.8)	53.1 (29.0)	.037
FOP (Av Std Ref Adj)	0.04 (0.02)	0.05 (0.03)	0.04 (0.02)	.2015
MtDNA (rel copy number)	3.2 (0.83)	3.15 (0.73)	3.19 (0.88)	.7746
Blood pressure				
SBP (mmHg)	124.0 (14)	132.7 (14.1)	119.7 (11.7)	<.0001
DBP (mmHg)	76.3 (9.2)	78.9 (9.6)	75.1 (8.7)	.0004
BMI (kg/m^2)	29.8 (6.6)	33.0 (6.7)	28.4 (5.9)	<.0001

AA, African Americans; Av Std Ref Adj, average standard reference adjusted; BMI, body mass index; DBP, diastolic blood pressure; F_2-isoP, F_2-isoprostanes; FOP, fluorescent oxidative products; γ-Toc, gamma tocopherol; MtDNA, mitochondrial DNA copy number; NSAIDs, nonsteroidal anti-inflammatory drugs; NHW, Non-Hispanic Whites; OBS, oxidative balance score; SBP, systolic blood pressure; WAI, West African Immigrants.

For continuous variables, *t* test was used to test the difference between hypertensive and normotensives, whereas chi-square test was used for categorical variables.

Table 3

Correlations between OS markers and OBS

Marker	FOP	F_2-isoP	MtDNA	γ-Toc	OBS
FOP	1	−0.32*	−0.02	−0.15*	0.37*
F_2-isoP	−0.17*	1	−0.15	0.40*	−0.11
MtDNA	−0.01	−0.14	1	−0.12	−0.10
γ-Toc	−0.15*	0.36*	−0.15	1	−0.02
OBS	0.31*	−0.16	−0.09	−0.01	1

F2-isoP, F2-isoprostanes; FOP, florescent oxidation products; γ-Toc, gamma tocopherol; MtDNA, mitochondrial DNA copy number; OBS, oxidative balance score.

Spearman are above diagonal, and Pearson are below the diagonal.

*$P < .05$.

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Table 4

The association between hypertension and FOP, F_2-isoP, MtDNA, γ-Toc, and OBS

Marker	Method 1	Method 2
	AOR	AOR
FOP		
Low	Ref	Ref
High	2.11 (0.88–5.06)	1.69 (0.92–2.53)
FOP (continuous, per 1-SD)	1.49 (0.89–2.51)	1.58 (0.96–2.20)
F_2-isoP		
Low	Ref	Ref
High	0.75 (0.27–2.06)	0.74 (0.35–1.55)
F_2-isoP (continuous, per 1-SD)	0.94 (0.53–1.67)	0.99 (0.98–1.01)
MtDNA		
Low	Ref	Ref
High	1.86 (0.62–5.63)	1.13 (0.75–1.71)
MtDNA (continuous, per 1-SD	0.94 (0.53–1.65)	1.04 (0.67–1.61)
γ-Toc		
Low	Ref	Ref
High	1.20 (0.51–2.82)	1.03 (0.67–1.58)
γ-Toc (continuous, per 1-SD)	0.93 (0.60–1.43)	0.32 (0.01–21.60)
OBS		
Low (2–8)	Ref	Ref
Medium (9–14)	0.30 (0.13–0.72)	0.89 (0.53–1.49)
High (15–22)	0.17 (0.03–0.95)	0.56 (0.22–1.43)
Continuous	0.87 (0.79–0.96)	0.91 (0.84–0.99)

AOR, adjusted odds ratio, controlling for age, sex, race or origin, education (smoking, aspirin use, and BMI) (when predictor was not OBS)—each biomarker was dichotomized based on sex and race- or origin-specific median; BMI, body mass index; continuous, per 1-SD, continuous variable scaled to 1 standard deviation; F_2-isoP, F_2-isoprostanes; FOP, fluorescent oxidative products; γ-Toc, gamma tocopherol; Method 1, original data used pairwise deletion; Method 2, used multiple imputation to handle missing data; MtDNA, mitochondrial DNA copy number.