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Relation of Changes in Body Fat Distribution to Oxidative Stress

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Abstract

Android fat is a surrogate measure of visceral obesity in the truncal region. Both visceral adiposity and oxidative stress (OS) are linked to cardiometabolic risk factors and clinical cardiovascular disease. However, whether body fat distribution (android vs gynoid) is associated with OS remains unknown. We hypothesized that increased android fat will be associated with greater OS. Body fat distribution and markers of OS, including plasma levels of reduced (cysteine and glutathione) and oxidized (cystine and glutathione disulfide) aminothiols, were estimated in 711 volunteers (67% female, 23% black, mean age 48 ± 11) enrolled in the Emory Georgia Tech Predictive Health study. At 1 year, 498 subjects had repeat testing. At baseline, anthropometric and fat distribution indexes, including body mass index, waist circumference, weight/hip ratio, and android and gynoid fat mass correlated with lower plasma concentrations of glutathione and higher cystine levels indicative of higher OS. At 1 year, the change in android but not gynoid fat mass or body mass index negatively correlated with the change in the plasma glutathione level after adjustment for cardiovascular risk factors. Increased body fat, specifically android fat mass, is an independent determinant of systemic OS, and its change is associated with a simultaneous change in OS, measured as plasma glutathione. In conclusion, our findings suggest that excess android or visceral fat contributes to the development of cardiovascular disease through modulating OS.

Oxidative stress (OS) may be defined as the occurrence of macromolecular damage from free radicals and the disruption of thiol, leading to dysfunctional redox control.[1] OS contributes to the pathophysiology of cardiovascular disease (CVD), partly through the inactivation of nitric oxide, resulting in endothelial dysfunction. Increased OS can be estimated as lower levels of circulating glutathione, an increased level of cystine, or a higher ratio of oxidized to reduced aminothiols.[1] Although body mass index (BMI) is an often used

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Disclosures

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Supplementary Data

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measure of adiposity, there is substantial variation in regional fat accumulation across BMI values in individual subjects.[2] Several studies have explored cross-sectional relations between fat distribution and various measurements of OS.[3] However, whether changes in gynoid versus android fat are associated with simultaneous changes in OS over time is unknown. Our aim in the present study was to evaluate the effect on systemic OS of temporal changes in android and gynoid fat mass in a study of subjects enrolled in a lifestyle intervention study. Our hypothesis was that decreases in abdominal (android) fat mass will be associated with lowering of OS.

Methods

Working adults without recent acute illnesses (n = 711) who were largely university employees were recruited by advertisement and selected by invitation as part of the Predictive Health Initiative (http://predictivehealth.emory.edu) from December 2007 to December 2010. Subjects visited the Emory-Georgia Tech Center for Health Discovery and Well Being for detailed phenotyping as previously outlined.[4] At the baseline visit, each subject was assigned a health partner, a subject who was specifically trained to utilize the subjects' data profiles and develop health-related goals and a personalized action plan at each visit. Subjects with an acute illness, hospitalization within the past year, pregnant women, and subjects with poorly controlled medical conditions were excluded. Subjects were followed up with comprehensive evaluations at baseline and after 1 year (n = 498). The study was approved by the Emory University Institutional Review Board and informed consent was obtained from all subjects.[5] At the baseline visit, each subject was assigned 1 of 6 health partners, individuals who were specifically trained to utilize subjects' data profiles and to collaboratively generate a health goal and personalized action plan at each visit.[4] Details of the HP intervention are described in the supplement section (Appendix S1). BMI was calculated as weight in kilogram/(height in meter).[2] Waist and hip circumferences were measured in centimeters by 2 measurements of the circumference with the recorded measurement representing the mean of the two. Waist/hip ratio was defined as the ratio of the waist-to-hip circumference. Body composition variables were calculated by dual-energy x-ray absorptiometry (iDXA, GE Lunar Densitometry, General Electric Company, Boston, MA/USA) that is considered to be a gold standard measure for the identification of whole-body fat mass within 2% coefficient of variation. The android region included an area from the top of the iliac crest to 20% of the distance from the iliac crest to the bottom of the subject's head. The gynoid region extended from the top of the greater trochanter down a distance twice the height of the android region.[6]

Hypertension, hypercholesterolemia, and diabetes mellitus were defined according to the Joint National Committee, Adult Treatment Panel III and American Diabetes Association criteria, respectively, and smoking habits were recorded.[7–9] Tobacco use was self-reported and categorized by questionnaire on each examination. Fasting lipid profile, metabolic panel, and C-reactive protein (CRP) (Quest Diagnostics, Madison, New Jersey) levels were measured at each visit.

Plasma cysteine, its oxidized form cystine, glutathione, and its oxidized form, glutathione disulfide, were measured in all subjects using high-performance liquid chromatography-

mass spectrometry as previously described.[10] Lower levels of circulating glutathione or increased levels of cystine indicate a higher OS. Briefly, venous blood was transferred immediately into preprepared Eppendorf tubes containing preservatives to retard auto-oxidation, centrifuged, and stored at −80°C for no more than 2 months before transfer to the laboratory. Analyses by high-performance liquid chromatography were performed after dansyl derivatization on a 3-aminopropyl column with fluorescence detection. Metabolites were identified by coelution with standards and were quantified by integration relative to the internal standard, with validation relative to external standards as previously described.[11] Ratios of oxidized to reduced aminothiols (cystine/glutathione) were obtained directly.

Study variables are described as the mean ± standard deviation (unless otherwise specified) for continuous variables or as counts and proportions for categorical variables. Group differences were evaluated by Student *t* tests and proportional differences by 2-proportion z tests. Multivariate linear regression models were constructed to determine relations between measurements of fat distribution and measurements of OS after adjusting for age, gender, ethnicity, tobacco use, hypertension, diabetes, high-density lipoprotein (HDL), total cholesterol, and CRP. At 1 year of follow-up, univariate analysis was performed using the Pearson correlation coefficient, in addition to multivariate analysis using linear regression models to determine the relations between the change in the measurement of fat distribution and the change in the measurement of OS. Statistical analyses were conducted with Statistical Package for Social Sciences 23 (IBM SPSS, Inc., Chicago, Illinois).

Results

The demographic and clinical characteristics of the 711 baseline cohorts and 498 who had been prospectively followed up are presented in Table 1. The sample was 66% female and 72% white, with a mean age of 48 ± 11 years; 34% had a reported history of hypertension, 16% had hyperlipidemia, and 6% were smokers. The mean BMI was 27.8 kg/m^2 and the waist/hip ratio was 0.83 (Table 1). Android and gynoid fat mass were higher in blacks and in those with hypertension and diabetes mellitus, and in those with elevated triglyceride and low-density lipoprotein levels and lower HDL levels. However, only android mass was higher with increasing age and in smokers, whereas only gynoid mass was higher in women. Android and gynoid fat mass were also highly correlated with each other and with BMI and waist circumference (Supplementary Table S1).

At baseline, all measurements of adiposity correlated negatively with glutathione and positively with cystine levels and the cystine/glutathione ratio, suggesting the presence of higher systemic OS in those with increased adiposity (Table 2). Multivariate analyses were performed to investigate whether these associations were independent of covariates, including age, gender, race, mean arterial pressure, total cholesterol, HDL, and CRP levels, history of diabetes, and smoking (Table 3). After adjustment for these cardiovascular risk factors and with gynoid and android fat mass in the same model, only android fat remained correlated negatively with glutathione and positively with the cystine/glutathione ratio, whereas gynoid fat was only positively associated with the cystine level (Table 3).

After 1 year, the 498 subjects who had returned for repeat testing had lost a mean of 1.3 kg (2.9 lb) in weight with simultaneous reductions in BMI, waist circumference, waist/hip ratio, and android and gynoid fat mass. The subjects also had lower systolic and diastolic blood pressures and lower total cholesterol and low-density lipoprotein levels. This finding was accompanied by a significant reduction in glutathione levels, indicating increased OS in the entire group after 1 year (Table 1). However, the change in BMI, android fat mass, and the android/gynoid ratio were all correlated inversely with the change in glutathione level, suggesting that reductions in android rather than gynoid fat mass were associated with a reduction in OS (Table 4). Even after adjustment for changes in BMI and gynoid fat mass at 1 year, both the changes in android fat mass and the android/gynoid ratio remained negatively correlated with changes in glutathione levels ($\beta = -0.110$, $p = 0.022$, and $\beta = -0.134$, $p = 0.005$, respectively) (Supplementary Table S2). Further adjustment for subjects who started on a statin, antihypertensive, or diabetic medication during follow-up and changes in age, tobacco use, diabetes, blood pressure, total cholesterol and HDL, and CRP at 1 year did not alter the results substantially (Supplementary Table S2). This finding indicates that decreases in android rather than gynoid fat mass were associated with the lowering of OS over time. Additional analyses demonstrated a positive correlation between the change in CRP and the change in BMI after 1 year; however, there was no significant correlation with changes in the android or gynoid fat mass or the android/gynoid ratio and the changes in CRP.

Discussion

In one of the largest studies analyzing the relations between OS and fat distribution measured by dual-energy x-ray absorptiometry in a community-based asymptomatic population, we demonstrated that higher android rather than gynoid fat correlates positively with systemic OS, independent of traditional cardiovascular risk factors and inflammation. In addition, a reduction in android fat mass, but not in gynoid fat or BMI, was associated with decreases in OS after 1 year of follow-up. These findings indicate that specific fat distribution and its changes rather than other estimates of obesity are associated with OS and thus provide further understanding regarding the relation between obesity and risk of CVD.

Several epidemiological and clinical studies have previously demonstrated the relation between obesity and other makers of OS and inflammation.[12] In adults and in children, obesity and higher total body fat is associated with higher urinary F2-isoprostane levels.[13,14] An inverse relation between total antioxidant capacity and body fat was observed in 3,042 adults.[15] In a lean subject population, various markers of OS and inflammation were associated with BMI and central adiposity, measured by waist circumference.[16] Our study supports and extends previous findings of a linear positive correlation between obesity and OS, and highlights the relations between android fat deposition and increased OS. However, the impact of changes in central or android obesity rather than general weight on OS remains unclear. Herein, we demonstrate that changes in android fat mass rather than gynoid fat mass are associated with changes in OS over time.

Experimentally, obesity is believed to be a state of chronic systemic OS that is characterized by an unbalanced redox status and altered antioxidant defenses.[17] Accumulation of

adipocytes leads to the generation of reactive oxygen species through NADPH oxidase activation that dysregulates expression of inflammatory adipocytokines, including adiponectin, plasminogen activator inhibitor-1, interleukin-6, and monocyte chemotactic protein-1,[18] and the decreased production of antioxidative enzymes.[19] Increased inflammatory and reduced anti-inflammatory cytokines mediate metabolic and cardiovascular disorders including insulin resistance, diabetes, and atherosclerosis through OS to endothelial cells. Furthermore, OS reduces nitric oxide bioavailability in endothelial cells and causes dysregulation of blood flow, with a subsequent impairment of lipid metabolism and of insulin regulation.[20]

OS has been linked to adverse outcomes in CVD. Furthermore, plasma aminothiols cystine and glutathione and their ratio are also associated with the risk of future death in a high-risk population with coronary artery disease independent of inflammation.[10] Mitochondrial dysfunction and increased reactive oxygen species production have been linked to early atherosclerosis.[21] OS is an important component of degenerative processes associated with aging.[22] The OS hypothesis of aging posits that macromolecular damage is due to the redox imbalance from higher OS over time.[23] Our study shows a significant decrease in the glutathione level after a year as we previously reported with aging.[22] Importantly, in those who lost android fat, the glutathione level increased over the year, reversing the age-associated decrease in the remaining population.

Lifestyle changes, including diet and physical activity, are beneficial in alleviating inflammation and improving OS in obese subjects. Weight loss induced by dietary caloric restriction decreased OS and improved the metabolic syndrome.[24] Plasma adipokine levels (CRP, leptin, and tumor necrosis factor alpha) and urinary markers of OS (8-hydroxy-2-deoxyguanosine and 8-isoprostanes) have been reported to improve with aerobic exercise even *without* a significant change in body composition in obese subjects.[25,26] Our data confirm these findings in a relatively healthy group of subjects exposed to a health partner intervention. In a previous study on this cohort, we have shown that ideal health metrics, including weight, insulin resistance, and blood pressure, were preserved in otherwise healthy subjects with the presence of CVD risk factors over time.[4] However, questions regarding changes in fat distribution rather than weight alone with lifestyle interventions remained unclear. In the present study, we demonstrate for the first time that a specific decrease in android, but not gynoid, adiposity induced by changes in lifestyle behaviors improves OS.

One of the limitations of our study is that it was conducted in a predominantly middle-aged employed population, and thus our findings may not apply to other populations. Several subjects were lost to follow-up for a variety of reasons, including relocation. However, there were no demographic differences between those who completed the follow-up and those who were lost to follow-up. In conclusion, body fat distribution, specifically android fat mass, is an independent determinant of OS measured as plasma glutathione level. The reduction in android adiposity with lifestyle intervention was the key driver for the improvement in these OS measurements, implying that excess android fat contributes to the development of OS.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Subject characteristics

Variable	Baseline characteristics* (n = 711)	Baseline follow-up* (n = 498)	One-year follow-up (n = 498)	p-value
Age (years)	48 ± 11	49 ± 11	50 ± 11	**<0.001**
Women	66 (%)	64 (%)	64 (%)	—
White	72 (%)	73 (%)	73 (%)	—
Black	23 (%)	22 (%)	22 (%)	—
Other Ethnicity	6 (%)	5 (%)	5 (%)	—
Hypertension	34 (%)	34 (%)	36 (%)	0.004
Hyperlipidemia	16 (%)	18 (%)	21 (%)	**0.01**
Current Tobacco Use	6 (%)	6 (%)	4 (%)	**0.011**
Diabetes	11 (%)	11 (%)	13 (%)	**0.007**
10-year Atherosclerotic Cardiovascular Disease risk	4.6 (%)	4.6 (%)	4.5 (%)	0.088
Systolic blood pressure (mmHg)	121 ± 16	121 ± 16	116 ± 15	**<0.001**
Diastolic blood pressure (mmHg)	76 ± 11	77 ± 15	74 ± 11	**<0.001**
Mean arterial pressure (mmHg)	91 ± 12	91 ± 11	88 ± 11	**<0.001**
Total cholesterol (mg/dL)	194 ± 36	194 ± 36	188 ± 35	**<0.001**
Triglycerides (mg/dL)	103 ± 60	104 ± 65	103 ± 57	0.465
High-density lipoprotein cholesterol (mg/dL)	63 ± 18	63 ± 18	62 18	**0.001**
Low-density lipoprotein cholesterol (mg/dL)	110 ± 32	111 ± 32	105 ± 30	**<0.001**
Height (cm)	169 ± 9.0	169 ± 9.0	169 ± 9.1	0.47
Weight (kg)	79.5 ± 19.7	79.1 ± 19.5	77.8 ± 19.1	**<0.001**
Body mass index (kg/m^2)	27.8 ± 6.4	27.6 ± 6.1	27.1 ± 5.9	**<0.001**
Waist Circumference (cm)	87.5 ± 15.8	87.2 ± 15.5	85.6 ± 13.8	**<0.001**
Waist:hip ratio	0.83 ± 0.09	0.83 ± 0.10	0.82 ± 0.09	**<0.001**
Android Fat Mass (kg)	2.76 ± 1.52	2.73 ± 1.49	2.63 ± 1.45	**<0.001**
Gynoid Fat Mass (kg)	5.66 ± 2.36	5.57 ± 2.27	5.44 ± 2.26	**<0.001**
C-Reactive Protein (mg/L)	2.76 ± 4.19	2.38 ± 3.81	2.38 ± 3.81	0.932
Cysteine (μM)	9.35 ± 2.18	9.30 ± 2.16	9.46 ± 2.13	0.193
Cystine (μM)	84.5 ± 17.9	85 ± 18.3	86.4 ± 18.2	0.077
Glutathione (μM)	1.73 ± 0.67	1.73 ± 0.65	1.61 ± 0.58	**<0.001**
Glutathione disulfide (μM)	0.06 ± 0.047	0.06 ± 0.05	0.07 ± 0.07	0.376
Cystine:Glutathione ratio	56.9 ± 29.5	56.7 ± 26.7	60.6 ± 26.8	**0.003**

*Values shown are mean ± SDs or number (percentage) for normally distributed variables or median [interquartile range] for non-normally distributed variables. Bold values indicate statistically significant difference (P < .05).

Table 2

Bivariate relationships between measures of adiposity and oxidative stress at baseline *

	Cysteine		Cystine		Glutathione		Glutathione disulfide		Cystine:Glutathione ratio	
	R	p-value	R	p-value	r	p-value	r	p-value	r	p-value
Body mass index	0.121	**0.002**	0.400	**<0.001**	−0.271	**<0.001**	−0.075	0.050	0.423	**<0.001**
Waist Circumference	0.082	**0.038**	0.352	**<0.001**	−0.246	**<0.001**	−0.083	**0.032**	0.396	**<0.001**
Waist:Hip Ratio	−0.033	0.399	0.163	**<0.001**	−0.160	**<0.001**	−0.040	0.300	0.215	**<0.001**
Total Fat	0.140	**<0.001**	0.379	**<0.001**	−0.249	**<0.001**	−0.067	0.081	0.400	**<0.001**
Gynoid Fat	0.147	**<0.001**	0.335	**<0.001**	−0.189	**<0.001**	−0.075	0.053	0.334	**<0.001**
Android:Gynoid Ratio	−0.020	0.618	0.200	**<0.001**	−0.208	**<0.001**	−0.048	0.218	0.239	**<0.001**
Android Fat	0.109	**0.006**	0.380	**<0.001**	−0.277	**<0.001**	−0.093	**0.016**	0.414	**<0.001**

* p Value was calculated using Pearson correlation.

Table 3

Multivariable Analyses between measures of adiposity and oxidative stress at baseline*

	Cysteine		Cystine		Glutathione		Glutathione disulfide		Cystine:Glutathione ratio	
	B	**p-value**	**β**	**p-value**	**β**	**p-value**	**B**	**p-value**	**β**	**p-value**
Gynoid Fat Mass	0.053	0.550	0.221	**0.003**	−0.002	0.979	−0.020	0.820	0.121	0.122
Android Fat Mass	0.043	0.627	0.071	0.337	−0.249	**0.003**	−0.122	0.162	0.227	**0.004**

Multivariate models controlling for gynoid fat mass, android fat mass, age, gender, race, diabetes, tobacco use, mean arterial pressure, total cholesterol, high-density lipoprotein cholesterol and C-reactive protein with measures of adiposity.

*p Value was calculated using linear regression.

Table 4

Relationships between changes in measures of adiposity and measures of oxidative stress during 1-year follow-up*

	ΔCysteine		ΔCystine		ΔGlutathione		Δ Glutathione disulfide		Δ Cystine:Glutathione ratio	
	R	p-value	R	p-value	r	p-value	r	p-value	r	p-value
ΔBMI	0.001	0.977	0.015	0.750	−0.094	**0.046**	0.007	0.885	0.045	0.339
ΔWaist Circumference	0.021	0.662	−0.006	0.901	−0.021	0.654	−0.026	0.587	0.001	0.989
ΔWaist:Hip Ratio	0.017	0.730	−0.007	0.885	−0.029	0.539	−0.059	0.214	0.025	0.596
ΔTotal Fat	0.008	0.867	−0.016	0.727	−0.113	**0.017**	−0.001	0.979	0.076	0.108
ΔGynoid Fat	0.043	0.370	−0.025	0.600	−0.077	0.110	0.009	0.844	0.051	0.294
ΔAndroid Fat	0.030	0.543	−0.031	0.517	−0.133	**0.006**	−0.006	0.893	0.086	0.073
ΔAndroid:Gynoid Ratio	0.012	0.808	−0.014	0.769	−0.129	**0.007**	−0.043	0.373	0.066	0.170

*p Value was calculated using Pearson bivariate correlation.