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Oxidative Stress Is Associated with Greater Mortality in Older Women Living in the Community

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Abstract

Objectives—To determine whether oxidative stress, as implied by oxidative damage to proteins, is associated with greater mortality in older women living in the community.

Design—Longitudinal.

Setting—Women's Health and Aging Study I, Baltimore, Maryland.

Participants—Seven hundred forty-six moderately to severely disabled women, aged 65 and older, with baseline measures of serum protein carbonyls.

Measurements—Serum protein carbonyls, which consist of chemically stable aldehyde and ketone groups produced on protein side chains when they are oxidized, were measured using enzyme-linked immunosorbent assay. Multivariate logistic regression was used to adjust for potential confounders.

Results—During 5 years of follow-up, 202 (27.1%) participants died. Geometric mean serum protein carbonyls were 0.091 nmol/mg in women who died and 0.083 nmol/mg in those who survived ($P = .02$). Log_e protein carbonyls (nmol/mg) were associated with greater risk of mortality (hazards ratio = 1.34, 95% confidence interval = 1.01–1.79, $P = .04$) in a multivariate Cox proportional hazards model adjusting for age, current smoking, and body mass index.

Conclusion—Greater oxidative stress, as indicated by elevated serum protein carbonyl concentrations, was associated with greater risk of death in older women living in the community who were moderately to severely disabled. Prevention of oxidative stress may reduce the risk of mortality.

Keywords

aging; mortality; oxidative stress; protein carbonyls; women

Denham Harman proposed the free radical theory of aging in 1956,¹ which has become one of the main theories of aging. The theory postulates that the damage from reactive oxygen

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species to deoxyribonucleic acid (DNA), protein, and lipids increases with age and that this damage accumulates and contributes to senescence. Reactive oxygen (O_2) species are ubiquitous reactive derivatives of O_2 metabolism that are found in all biological systems, and they are formed as intermediates in reduction-oxidation (redox) processes that lead from oxygen to water. Major intracellular sites for generation of reactive oxygen species are mitochondria, and exogenous sources include cigarette smoke and ultraviolet radiation.² Among the major reactive oxygen species are superoxide, hydrogen peroxide, hydroxyl radical, fatty acid peroxy radical, nitric oxide, and peroxynitrite.² Antioxidant defenses that include antioxidant enzymes such as superoxide dismutase, catalase, thioredoxin, and glutathione peroxidase and exogenous antioxidants such as carotenoids, tocopherols, ascorbate, selenium, flavonoids, and other plant polyphenols balance reactive oxygen species. Oxidative stress refers to the condition in which the balance between oxidants and antioxidant defenses is upset and excess reactive oxygen species cause oxidative damage to nucleic acids, proteins, and lipids.

A growing body of evidence that shows that low levels of exogenous antioxidants are associated with a higher risk of death^{3,4} and that oxidative damage increases with aging in animal models² supports the free radical theory of aging. Reactive oxygen species have an extremely short half-life and are difficult to measure in humans, but it is possible to measure the damage they cause to protein, lipids, and DNA. The relationship between oxidative stress, as measured according to oxidative damage to proteins, and mortality has not been well characterized in older adults. Protein carbonyls are the most studied marker of protein oxidation.⁵ Protein carbonyls represent several pathways of oxidative protein damage and are useful in epidemiological studies, because they are stable and can be measured in serum or plasma.⁵ Protein carbonyls have a major advantage over lipid peroxidation products as markers of oxidative stress, because oxidized proteins are generally more stable.⁵ It was hypothesized that higher oxidative stress, as indicated by serum protein carbonyl levels, was associated with a greater risk of death in older adults. To address this hypothesis, the relationship between serum protein carbonyl concentrations and mortality in older women living in the community was examined.

Methods

Subjects in this study were women aged 65 and older who participated in the Women's Health and Aging Study I (WHAS I), a population-based study designed to evaluate the causes and course of physical disability in older women living in the community. WHAS I participants were recruited from an age-stratified random sample of women aged 65 and older selected from Medicare enrollees residing in 12 contiguous ZIP code areas in Baltimore.⁶ Women were screened to identify self-reported physical disability that was categorized into four domains. The domains of disability were ascertained in a 20- to 30-minute home interview that included questions related to mobility and exercise tolerance (walking for a quarter of a mile, walking up 10 steps without resting, getting in and out of bed or chairs), upper extremity function (raising arms up overhead, using fingers to grasp or handle, lifting or carrying something as heavy as 10 pounds), higher-functioning tasks (a subset of instrumental activities of daily living, not including heavy housework: using the telephone, doing light housework, preparing meals, shopping for personal items), and basic self-care tasks (a subset of nonmobility-dependent activities of daily living: bathing or showering, dressing, eating, using the toilet). WHAS I enrolled the one-third most-disabled women aged 65 and older—those with disability in two or more domains. Of the 1,409 women who met study eligibility criteria, 1,002 agreed to participate in the study in 1992. There were no major differences in sociodemographic or reported health characteristics between eligible participants and those who declined to participate.⁶

Trained interviewers administered standardized questionnaires in the participant's home. Race was assessed in a questionnaire as black, white, or other; current smoking as yes or no; and education as 0 to 8, 9 to 11, 12, or more than 12 years as the highest level of formal education achieved. Two weeks later, a trained, registered, full-time study nurse conducted an examination of each study participant in her home, using a standardized protocol that included physical performance measures and a standardized physical examination. Approximately 75% of the women also consented to phlebotomy performed during a separate visit by a trained phlebotomist who followed a standardized protocol. Chronic diseases were diagnosed using adjudication and standardized algorithms.⁶ Further details on the methods and sampling design of the WHAS studies have been published elsewhere.⁶

There were 1,002 women enrolled in the Women's Health and Aging Study I, of whom 746 participated in the blood drawing and had serum protein carbonyl measurements at baseline. There were no significant differences in race or body mass index (BMI) between those who did and did not participate in the blood drawing, but there was a difference in age (77.4 vs 80.7, $P < .001$). Nonfasting blood samples were obtained using venipuncture between 9 a.m. and 2 p.m. Processing, aliquoting, and freezing were performed at the Core Genetics Laboratory of The Johns Hopkins University School of Medicine following a standardized protocol. Blood samples were delivered to Quest Diagnostics Laboratories (Teterboro, NJ) and stored continuously at -70°C until the time of analyses for serum protein carbonyls. Serum protein carbonyls were measured using a commercial enzyme-linked immunosorbent assay (ELISA, Zentech PC Test, Protein Carbonyl Enzyme Immuno-Assay Kit, Zenith Technologies, Dunedin, New Zealand). Protein carbonyls are stable under long-term storage at -70°C .⁵ The assay has a minimum detectability of 0.02 nmol/mg protein, which is well below the range found in healthy human controls. Intra-assay and interassay coefficients of variation for protein carbonyl measurements were 10.1% and 18.2%, which is within the acceptable range for a serological assay such as ELISA.⁷

Vital status was determined on all women for whom baseline data on protein carbonyls was obtained through follow-up telephone interviews with living subjects, interviews with proxies, obituaries, and matching with the National Death Index from the baseline visit, 1992 to 1995 through the end of 2000. The Johns Hopkins University institutional review board approved the study protocol, and written informed consent was obtained from all participants.

Categorical variables were compared between groups using chi-square tests. Continuous variables were compared between groups using the Student *t*-test, and serum protein carbonyls were log-transformed to achieve a normal distribution. BMI was categorized as underweight ($<18.5 \text{ kg/m}^2$), normal range ($18.5\text{--}24.9 \text{ kg/m}^2$), overweight ($25.0\text{--}29.9 \text{ kg/m}^2$) and obese ($\geq 30.0 \text{ kg/m}^2$) according to World Health Organization criteria.⁸ Cox proportional hazards models were used to examine the relationship between serum protein carbonyls and 5-year all-cause mortality. All analyses were conducted using SAS (SAS Institute, Inc., Cary, NC).

Results

During 5 years of follow-up, 202 (27.1%) of 746 participants died. Demographic and other characteristics of women who died or survived are shown in Table 1. Women who died were older and were more likely to have a low BMI; be a current smoker; and have congestive heart failure, peripheral artery disease, diabetes mellitus, and depression. There were no significant differences between groups according to race, education, or proportion with hypertension, coronary artery disease, stroke, chronic obstructive pulmonary disease, or cancer. Geometric mean serum protein carbonyls were 0.091 nmol/mg in women who died and 0.083 nmol/mg in those who survived ($P = .02$).

Univariate and multivariate Cox proportional hazards models for $\log_e$ protein carbonyls and mortality are shown in Table 2. In a univariate analysis (Model 1), $\log_e$ protein carbonyls (nmol/L) were associated with greater risk of mortality (hazard ratio (HR) = 1.34, 95% confidence interval (CI) = 1.05–1.80, $P = .04$). In a multivariate model adjusting for age (Model 2), $\log_e$ protein carbonyls were associated with greater risk of mortality (HR = 1.40, 95% CI = 1.05–1.85, $P = .02$). In a final multivariate model adjusted for age, BMI, and current smoking (Model 3), $\log_e$ protein carbonyls (nmol/L) were associated with greater risk of mortality (HR = 1.34, 95% CI = 1.01–1.79, $P = .04$).

Alternative models were explored that included variables that are considered to be in the causal pathway between oxidative stress and mortality. In a model adjusting for congestive heart failure, peripheral artery disease, diabetes mellitus, renal disease, and depression in addition to the variables included in Model 3, the relationship between protein carbonyls and mortality was only slightly attenuated (HR = 1.22, 95% CI = 0.90–1.64, $P = .19$). In a model adjusting for interleukin (IL)-6 in addition to age, smoking, and BMI, the relationship between protein carbonyls and mortality was only slightly attenuated (HR = 1.25, 95% CI = 0.94–1.67, $P = .12$).

Discussion

The present study shows that oxidative stress, as indicated by higher levels of oxidative protein damage, is a predictor of mortality in moderately to severely disabled older women living in the community. To the authors' knowledge, this is the first study to show that oxidative damage to proteins is associated with greater risk of death in a population of older adults. Oxidative stress is considered a basic underlying biological mechanism for atherosclerosis, coronary artery disease, diabetes mellitus, congestive heart failure, peripheral artery disease, stroke, Alzheimer's disease, sarcopenia, and many other common morbid conditions in older adults. The findings from the present study suggest that oxidative stress is a common unifying biological mechanism that may underlie the greater risk of mortality in older adults. Oxidative stress can compromise biological function in two general ways: by directly damaging protein, lipids, and DNA and by providing a trigger to redox-sensitive transcription factors that upregulate inflammatory cytokines.

Protein carbonyls have been shown to have construct validity in animal studies and epidemiological investigations. Animal studies show that ozone, ionizing radiation, hyperoxia, forced exercise, cigarette smoke, and other well-documented sources of reactive oxygen species will increase the levels of protein carbonyls in serum and tissues.⁹ In humans, elevated protein carbonyls have been described in conditions that are known to be associated with increased oxidative stress, such as Alzheimer's disease, cystic fibrosis, diabetes mellitus, and chronic renal failure.⁵ In humans, a high dietary intake of antioxidant-rich foods decreases serum protein carbonyls.⁹ Vigorous exercise increases serum protein carbonyls, and dietary antioxidant intake can modify this postexercise increase in protein carbonyls.¹⁰ The main limitation with using ELISA for measuring serum protein carbonyls is that this assay must be considered a broad marker of protein oxidation rather than a marker for oxidation of a specific protein.⁵

Oxidative damage to proteins can lead to loss of structural integrity of cells, compromise cellular function, and increase susceptibility to proteolysis.^{11–14} Oxidative damage to lipids, or lipid peroxidation, occurs when polyunsaturated fatty acids in cell membranes are exposed to reactive oxygen species, resulting in altered cell membrane structure, impaired function, and cell loss.¹⁵ Oxidative damage to DNA can result in single- and double-strand breaks; interstrand, intrastrand, and DNA-protein crosslinks; and other oxidation and fragmentation products.¹⁶ The present study is limited in that oxidative damage to lipids and DNA was not

measured. Studies are currently in progress to measure endogenous and oxidative DNA damage using single-cell gel electrophoresis (comet assay).

Reactive oxygen species can cause excessive oxidative damage to proteins when antioxidant defenses are impaired (i.e., low levels of exogenous antioxidants such as carotenoids, ascorbate, and polyphenols and endogenous antioxidants such as the selenoprotein glutathione peroxidase). Reactive oxygen species also trigger redox-sensitive transcription factors nuclear factor (NF)- κ B^{17,18} and activating protein-1^{18,19} that are involved in the upregulation of inflammatory cytokines such as IL-1 β , tumor necrosis factor (TNF)- α , and IL-6. The upregulation of inflammation from oxidative stress may contribute to the low-grade inflammatory state that is common in older adults.^{20,21} TNF- α , IL-1 β , IL-6, IL-18, C-reactive protein, and fibrinogen are among the cytokines and acute-phase proteins that may be elevated in this proinflammatory state.²¹ Low serum carotenoid levels, which represent the antioxidant side of the balance between antioxidants and reactive oxygen species, was predictive of subsequent elevations of IL-6 and greater mortality in this same cohort.²² In the present study, serum protein carbonyls now provide a missing part of this biological pathway that involves reactive oxygen species, inflammation, and mortality.

The proinflammatory state in older adults may contribute to a wide variety of pathological processes in older adults such as insulin resistance, dyslipidemia, coagulation, lymphocyte activation, atherosclerosis, osteoporosis, cognitive impairment, and mortality.^{20,21} Oxidative stress is the pathogenic mechanism that is common to all these processes, leading to what has been termed the “common soil” hypothesis.²³

In the present study, IL-6 was not included in the main multivariate models examining the relationship between protein carbonyls and mortality, because oxidative stress upregulates IL-6 through redox-sensitive NF- κ B and is in the pathway between oxidative stress and mortality. When IL-6 was included in the multivariate analyses, the relationship between protein carbonyls and mortality was slightly attenuated, as expected. The main multivariate analyses also did not include chronic diseases that are associated with greater oxidative stress and inflammation.

Congestive heart failure,⁵ peripheral artery disease,²⁴ diabetes mellitus,⁵ and depression²⁵ are associated with greater oxidative stress and inflammation. As expected, inclusion of these conditions slightly attenuated the relationship between protein carbonyls and mortality, because these conditions are in the causal pathway between oxidative stress and mortality.

If greater oxidative stress is shown definitively to be the basic process that underlies atherosclerosis, congestive heart failure, diabetes mellitus, Alzheimer's disease, and other morbidities, interventions aimed at reducing oxidative stress could potentially have broad benefits for older adults. Such interventions to reduce oxidative stress would include lowering sources of free radicals, (i.e., smoking cessation, reducing adipose mass through diet and exercise, and increasing intake of antioxidant-rich foods such as fruits and vegetables). Smoking is a well-known source of oxidative stress,⁵ and oxidative stress is higher in obese individuals.²⁶ A Mediterranean-style diet characterized by high dietary intake of fruits and vegetables^{27–29} and consumption of olive oil³⁰ is associated with lower oxidative stress.

The present study was conducted in moderately to severely disabled older women living in the community, and it is not certain whether these findings can be generalized to older men and to less-disabled older adults. A limitation of the study is that, like many longitudinal studies in older adults, the study addressed all-cause mortality and did not have a large-enough number of deaths to examine cause-specific mortality. Future studies are needed to determine whether high oxidative stress is associated with mortality in less-disabled community-dwelling older

adults and to gain insight into the role of lifestyle factors such as smoking, diet, and exercise in the reduction of oxidative stress.

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Table 1

Demographic and Health Characteristics of Women, Aged 65 and Older, in the Women's Health and Aging Study I in Baltimore, Maryland, Who Survived or Died During 5 Years of Follow-Up (N = 746)

Characteristic	Lived (n = 544)	Died (n = 202)	P-Value
Age, n (%)			
65–69	114 (21.9)	23 (11.4)	<.001
70–74	141 (25.9)	33 (16.3)	
75–79	107 (19.7)	34 (16.8)	
80–84	56 (10.3)	31 (15.4)	
85–89	98 (18.0)	55 (27.2)	
≥90	23 (4.2)	26 (12.9)	
White, n (%)	386 (70.9)	151 (74.7)	.30
Education <12 years, n (%)	350 (64.3)	139 (69.5)	.18
Current smoker, n (%)	58 (10.6)	32 (15.8)	.05
Body mass index, kg/m ² , n (%)			
<18.5	13 (48.1)	14 (51.8)	<.001
18.5–24.9	114 (67.9)	54 (32.1)	
25.0–29.9	173 (72.7)	65 (27.3)	
≥30.0	201 (82.4)	43 (17.6)	
Log _e protein carbonyls, mean	–2.48	–2.39	.02
Geometric mean protein carbonyls, nmol/mg, mean	0.083	0.091	.02
Hypertension, n (%)	319 (58.7)	116 (57.7)	.80
Coronary heart disease, n (%)	128 (23.5)	49 (24.3)	.83
Congestive heart failure, n (%)	43 (7.9)	37 (18.3)	<.001
Peripheral artery disease, n (%)	95 (17.3)	69 (34.1)	<.001
Stroke, n (%)	31 (5.7)	12 (5.9)	.90
Diabetes mellitus, n (%)	80 (14.7)	48 (23.8)	.004
Chronic obstructive pulmonary disease, n (%)	144 (26.5)	64 (32.2)	.12
Depression, n (%)	80 (14.7)	49 (24.3)	.002
Cancer, n (%)	56 (10.3)	28 (13.8)	.17
Renal disease, n (%)	37 (7.0)	28 (14.4)	.003

Table 2

Multivariate Logistic Regression Models of Protein Carbonyls and Other Risk Factors for Mortality in Women Aged 65 and Older in the Women's Health and Aging Study I in Baltimore, Maryland (N = 746)

Variable	HR	95% Confidence Interval	P-Value
Model 1			
Log _e protein carbonyls *	1.37	1.05–1.80	.02
Model 2			
Log _e protein carbonyls *	1.40	1.05–1.85	.02
Age			
65–69	1.00	—	—
70–74	1.24	0.72–2.11	.43
75–79	1.56	0.92–2.64	.1
80–84	2.66	1.55–4.57	<.001
85–89	2.60	1.59–4.22	<.001
≥90	4.10	2.33–7.18	<.001
Model 3			
Log _e protein carbonyls *	1.34	1.01–1.79	.04
Age			
65–69	1.00	—	—
70–74	1.21	0.71–2.07	.49
75–79	1.44	0.84–2.47	.18
80–84	2.60	1.50–4.50	<.001
85–89	2.66	1.48–4.07	<.001
≥90	3.78	2.09–6.84	<.001
Current smoking	1.66	1.22–2.47	.01
Body mass index, kg/m ²			
<18.5	1.26	0.71–2.25	.43
18.5–24.9	1.00	—	—
25.0–29.9	0.79	0.57–1.11	.17
≥30.0	0.61	0.41–0.90	.01

* Hazard ratio (HR) per 1 standard deviation increase in log_e protein carbonyls.