HHS Public Access

Author manuscript

J Am Geriatr Soc. Author manuscript; available in PMC 2018 June 01.

Published in final edited form as:

J Am Geriatr Soc. 2017 June ; 65(6): 1306–1309. doi:10.1111/jgs.14822.

Biology of falls: preliminary cohort study suggesting a possible role for oxidative stress

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Abstract

Background—Biological underpinnings of falls in older adults are not well established.

Objectives—To examine the validity of selected oxidative stress and inflammatory biomarkers for predicting incident falls in community dwelling older adults.

Design—Prospective cohort study.

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Conflict of Interest: None

Conflict of Interest Disclosures:

Elements of Financial/Personal Conflicts	*Author 1 J. Verghese		*Author 2 E. Ayers				
	Yes	No	Yes	No			
Employment or Affiliation		X		X			
Grants/Funds	x		x				
Honoraria		x		x			
Speaker Forum		x		x			
Consultant		x		x			
Stocks		x		x			
Royalties		x		x			
Expert Testimony		x		x			
Board Member		x		x			
Patents		x		x			
Personal Relationship		x		x			

For “yes” x mark(s): give brief explanation below: JV and EA received funding support from National Institute on Aging grants (R01 AG039330, R01AG044007, AGO44829 and R01AG036921).

Authors contribution: JV was responsible for study concept and design, interpretation of data, and preparation of manuscript. EA was responsible for data collection, analysis of data, and preparation of manuscript.

Sponsors role: The sponsor study had no role in the design and the collection, analysis, and interpretation of data and the writing of the article and the decision to submit it for publication.

Setting and Participants—266 non-demented and ambulatory community-dwelling older adults (mean age 78 years, 55% women).

Measurements—Oxidative stress (malondialdehyde) and inflammatory (interleukin-6 (IL-6)) biomarkers were selected based on associations with fall risk factors, and values were log-transformed to account for non-normal distributions.

Results—Over a mean follow-up of 20.5 ± 10.1 months, 119 participants fell. In Cox proportional hazards models, each one standard deviation increase in baseline log-malondialdehyde levels predicted incident falls (Hazard ratio adjusted for age, gender, education, comorbidity count, medications, log-IL-6 levels, prior falls, depressive symptoms, cognitive status, gait velocity and balance 1.53, 95% CI 1.11–2.16). Log-IL-6 levels were not associated with falls. Participants in the highest log-malondialdehyde quartile at baseline had increased risk for incident falls than those in the lowest quartile (HR 2.47, 95% CI 1.41–4.34).

Conclusion—Oxidative stress predicted falls in a community based cohort, and should be further examined as a fall risk biomarker as well as a potential target to prevent falls.

Keywords

Falls; Aging; oxidative stress; inflammation

INTRODUCTION

Falls are a major contributor to morbidity, disability and mortality in aging. While multiple clinical risk factors for falls have been identified,^{1–3} the biological underpinnings of falls are not established. Identifying specific biological derangements that lead to falls may open new avenues for developing interventions to prevent falls in older adults. Oxidative stress and inflammation are interlinked in aging,⁴ and are associated with increased risk of developing not only fall risk factors such as gait and cognitive impairment⁵ but also consequences of falls such as fractures.⁶ Yet, a definitive role for oxidative stress and inflammatory pathways in falls has not yet been proven. Our objective in this preliminary prospective cohort study was to examine the predictive validity of selected oxidative stress and inflammatory biomarkers for incident falls in community dwelling older adults.

METHODS

Participants

We studied community-residing adults age 65 and older enrolled in the “Central Control of Mobility in Aging” (CCMA) study.⁷ The objective of CCMA is to determine cognitive processes and brain substrates controlling mobility.^{7–10} CCMA procedures were previously described.^{7, 11, 12} In brief, research assistants interviewed potential participants by telephone to assess eligibility, and to rule out dementia using cognitive screeners.^{7–10} Individuals who passed the telephone interview and expressed interest in participating in the study were invited to in-person visits at our center.^{7–10} Dementia diagnoses were assigned at consensus case conferences.¹³ Exclusion criteria for CCMA were presence of dementia, inability to walk, active neurological or psychiatric disorders severe enough to interfere with study assessments, presence of major visual or hearing loss, and recent or planned surgical

procedures restricting walking. All participants provided written informed consents. The Einstein institutional review board approved the study protocol.

Of the 282 CCMA participants who were cross-enrolled into a new sub-study examining biological underpinnings of falls conducted between July 2013 and September 2014, 9 with dementia, 3 with Parkinson's disease, and 4 with oxidative stress levels > 4 standard deviations above the mean were excluded, leaving 266 individuals eligible for this analysis.

Falls assessment

Falls were prospectively assessed till August 2016. Falls were defined as unintentionally coming down on the floor or to a lower level not due to a major intrinsic or extrinsic event.¹⁴ Research assistants interviewed participants at yearly in-person visits and every 2–3 months in between the annual visits by telephone regarding the occurrence of any new falls since the last interview. A standardized falls questionnaire was used to ensure consistency between interviewers and over follow-up. If participants reported a fall, interviewers ascertained whether there were any associated injuries (such as fractures).

Biomarkers

Oxidative stress (malondialdehyde) and inflammatory (interleukin-6 (IL-6)) biomarkers were selected for this preliminary study based on reported associations with fall risk factors.^{5, 15, 16} Malondialdehyde is one of the most frequently used indicators of oxidative stress induced lipid peroxidation.⁴ Oxidative stress is linked to chronic inflammation in aging,⁴ which in turn has been linked to fall risk factors such as slow gait.¹⁵ Malondialdehyde (TBARS Assay Kit, Cayman Chemical, Ann Arbor, MI) and IL-6 (IL-6 Chemiluminescence ELISA Assay, Alpco, Salem, NH) was measured from frozen plasma and serum samples, respectively. Inter-assay coefficient of variation is 5.5% for malondialdehyde assays and 5% for IL-6 assays.

Covariates

Established fall risk factors identified from previous studies^{1–3} that were included as covariates in our analyses were history of previous falls, 9-point comorbidity count (presence or absence of diabetes, arthritis, hypertension, depression, chronic bronchitis, stroke, heart failure, angina, and myocardial infarction), gait velocity (cm/sec), balance (Unipedal stance, sec), medication count (prescription and non-prescription), general mental status (Repeatable Battery for the Assessment of Neuropsychological Status - total score), and depressive symptoms (30-item Geriatric depression scale). Participants were asked about prescription and non-prescription medications use at study visits, and requested to bring in medication lists, prescriptions, or medicine bottles for verification at study visits. We consulted medical records and contacted family members when available or physicians to verify or obtain further details of illnesses and medications.

Analysis

Biomarker values were log transformed as their distributions were skewed to the left. Malondialdehyde was examined both as a continuous variable and categorically in quartiles (lowest quartile was the reference group) in our analyses. The non-transformed quartile

ranges for malondialdehyde were <4.04, 4.04 to 5.30, 5.31 to 8.83, and >8.83 $\mu\text{mole/liter}$. The quartiles for IL-6 were <1.90, 1.90 to 2.69, 2.70 to 3.70, and >3.70 pg/ml. Values < 1.0 pg/ml, the lowest level of detection for IL-6, were included in all analyses as 1.0 pg/ml. Cox proportional hazard models were used to study the association of the selected biomarker levels at baseline with incident falls over follow-up, and was reported as Hazard Ratios (HR) adjusted for age, gender, education, and comorbidity count (Model 1). Time to event was from baseline to incident fall or to their final interview for participants who did not fall. Model 2 added the other fall risk factors described above and log-IL-6 levels to Model 1. Injurious falls, which may be less prone to recall bias,¹⁷ was examined as a secondary outcome to corroborate main findings. Proportional hazards assumptions of all models were tested graphically and analytically, and were adequately met.

Biomarker associations with fall rates were similar in this prospective cohort using negative binomial regression, and are not presented.

RESULTS

The mean age of participants was 78 years with 54% women. Table 1 provides baseline demographic and medical characteristics. The cohort was relatively healthy as indicated by the low comorbidity count, high cognitive scores and gait velocity. Over a mean follow-up of 20.5 ± 10.1 months, 119 participants reported falls (incidence rate 26/100 person-years). Compared to the 119 participants who fell over study follow-up, the 147 participants who did not fall were similar in age (non-fallers: 77.4 ± 6.3 years vs. fallers: 78.6 ± 6.8 years, $p = 0.136$), sex (non-fallers: 50% vs. fallers 59%, $p = 0.136$), and gait velocity (non-fallers: 98.1 ± 22.8 cm/sec vs. fallers: 97.9 ± 23.8 cm/sec, $p = 0.947$), but had significantly less disease burden (1.5 ± 1.0 vs. 1.8 ± 1.1 , $p = 0.028$). Median time to first fall was 11.0 months. Of the 119 incident falls, 74 (62.2%) were injurious and 65 (54.6%) fell more than once. Mean malondialdehyde and IL-6 levels at baseline were 7.2 ± 5.1 (range: 1.5–29.3) $\mu\text{mole/liter}$ and 3.5 ± 3.3 (range: 1.0–26.9) pg/mL, respectively.

Table 2 shows that each standard deviation increase in log-malondialdehyde levels predicted incident falls in Model 1 (HR 1.47) and Model 2 (HR 1.53). IL-6 was not associated with falls in both models. Participants in the highest log-malondialdehyde quartile had increased risk for falls compared to those in the lowest quartile in the fully adjusted model (HR 2.47, 95% CI 1.41–4.34, $p = 0.002$). The association of the second ($p = 0.349$) and third ($p = 0.108$) log-malondialdehyde quartiles with falls was not significant compared to the lowest quartile. The highest three quartile levels of IL-6 were also not associated with falls compared to the lowest quartile.

Each standard deviation increase in log-malondialdehyde levels also predicted risk for injurious falls (HR 1.69; 95% CI 1.13–2.55) in the fully adjusted model. Participants in the highest log-malondialdehyde quartile had over three-fold increased risk for injurious falls than those in the lowest quartile (HR 3.56; 95% CI 1.72–7.39). The association of the middle log-malondialdehyde quartiles with injurious falls was not significant. Figure 1 graphically depicts risk of falls associated with baseline malondialdehyde quartiles.

DISCUSSION

To our knowledge, this is the first report to associate oxidative stress to the risk of incident falls in aging. Our main finding was that each standard deviation increase in baseline log-malondialdehyde (which corresponds to a 1.7 times increase in untransformed malondialdehyde levels) in community dwelling and ambulatory older adults was associated with a 53% increased risk of incident falls in the fully adjusted models, which accounted for multiple potential confounders. Furthermore, participants in the highest log-malondialdehyde quartile in our cohort had an over two-fold increased risk for falls than those in the lowest quartile, suggesting a threshold effect of oxidative stress on falls. On the other hand, baseline IL-6 levels were not associated with falls in our analyses.

Our results are supported by previous studies that have reported that oxidative stress mechanisms are related to increased risk of developing several physical or cognitive impairments that lead to falls in older adults.^{18, 19} For instance, high oxidative stress predicted slowing in walking speed and development of severe walking disability in community dwelling older women.¹⁹ Investigators have also linked oxidative stress mechanisms to development of other fall risk factors such as cognitive impairment, frailty, and depressive symptoms.^{18, 20} Oxidative stress promotes chronic inflammation in aging, which in turn has effects on muscle and the nervous system.^{21, 22} However, the association of oxidative stress with falls was robust even after accounting for these various causes. Hence, while oxidative stress may lead to falls via its links with fall risk factors or peripheral inflammation, other as yet unexplored mechanisms also appear to contribute to the observed finding, and merits further study.

The prospective study design as well as the reliable clinical and statistical procedures are strengths.²³ Falls were prospectively ascertained in-person and by telephone. We have reported excellent test-retest reliability for fall self-reports using this protocol.³ Furthermore, our main findings were confirmed with injurious falls as a secondary outcome. Use of monthly falls calendars may improve outcome ascertainment. The biomarker panel was limited in this preliminary investigation, and a more in-depth examination of other oxidative stress markers as well as inflammatory markers in the context of falls is warranted.¹⁶ Specificity issues have been noted with the TBARS assay used in this study.²⁴ Furthermore, it is possible that differential relationships may be seen with falls may be seen with an expanded biomarker panel. Given the preliminary nature of this investigation, our findings as well as limitations identified will help design the next generation of studies exploring the biology of falls. If our findings are corroborated in future studies, reports that indicate that oxidative stress levels can be modulated by exercise, antioxidant therapy or diet indicate new avenues for developing novel fall prevention interventions.^{25, 26}

Oxidative stress should be further examined as a fall risk marker as well as a potential target to prevent falls.

Acknowledgments

Funding: This study was supported by the National Institute on Aging grants (RO1 AGO44007 and RO1 AG036921) and an intramural grant from the Resnick Gerontology Center, Albert Einstein College of Medicine, Bronx, NY, USA.

Funding: The CCMA study received funding from the National Institute on Aging (RO1AG044007 and RO1AG036921) and an intramural grant from Resnick Gerontology Center, Albert Einstein College of Medicine.

Thanks to the study clinicians, staff and participants of the CCMA study. We would like to thank Dr. Radhika Muzumdar and Dr. Zhenwei Gong at the University of Pittsburgh Medical Center for conducting the TBARS assays.

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Figure 1. Hazard function plot for the risk of incident falls by oxidative stress (Malondialdehyde) levels at baseline.

Table 1

Participant characteristics at baseline.

Variables	N = 266
Age (years)	78.0 ± 6.6
Female, n (%)	143 (53.8)
Education (years)	14.7 ± 3.2
Malondialdehyde concentration (μmole/liter)	7.2 ± 5.1
Interleukin-6 levels (pg/mL)	3.5 ± 3.3
Comorbidity count (range 0–9)	1.6 ± 1.0
Depression, n (%)	28 (10.5)
Diabetes, n (%)	49 (18.4)
Congestive Heart Failure, n (%)	2 (0.8)
Hypertension, n (%)	158 (59.4)
Myocardial Infarction, n (%)	13 (4.9)
Angina, n (%)	6 (2.3)
Stroke, n (%)	5 (1.9)
Chronic Obstructive Lung Disease, n (%)	19 (7.1)
Arthritis, n (%)	144 (54.1)
Medication count	4.4 ± 2.8
Fall in past year, n (%)	58 (21.8)
Geriatric Depression Score (range 0–30)	4.5 ± 3.7
RBANS *Total Score (range 0–100)	94.2 ± 12.5
Normal walking velocity (cm/sec)	98.0 ± 23.2
Unipedal stance time (sec)	11.6 ± 10.4

* RBANS: Repeatable Battery for the Assessment of Neuropsychological Status total score

Table 2

Oxidative stress concentration and risk of falls. See Methods for explanation of models.

Risk Factors	Model 1 (n = 266) HR (95% CI), p	Model 2 (n = 257) HR (95% CI), p
Malondialdehyde concentration (log-units)	1.47 (1.10–1.98), 0.010	1.53 (1.11–2.16), 0.010
Age (years)	1.03 (1.00–1.05), 0.054	1.02 (0.99–1.06), 0.227
Female	1.20 (0.82–1.75), 0.343	0.98 (0.65–1.47), 0.923
Education (years)	0.98 (0.93–1.04), 0.497	0.97 (0.91–1.03), 0.278
Comorbidity count (0–9)	1.20 (1.00–1.43), 0.050	1.15 (0.95–1.40), 0.159
Interleukin-6 (log-units)		0.82 (0.61–1.10), 0.192
Medications		1.01 (0.93–1.08), 0.884
Fall in past year		2.28 (1.45–3.59), <0.001
Geriatric Depression Score (0–30)		1.03 (0.97–1.08), 0.345
RBANS *Total Score		1.00 (0.98–1.02), 0.988
Normal walking velocity (cm/sec)		1.00 (0.99–1.01), 0.702
Unipedal stance time (sec)		1.00 (0.98–1.02), 0.824

* RBANS: Repeatable Battery for the Assessment of Neuropsychological Status total score