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Arterial stiffness and hand osteoarthritis: a novel relationship?

A. S. Saleh, M.B.B.S., M.P.H.[†], **S. S. Najjar, M.D.**[‡], **D. C. Muller, M.S.**[§], **V. Shetty, M.P.H.**[‡], **L. Ferrucci, M.D., Ph.D.**[§], **A. C. Gelber, M.D., M.P.H., Ph.D.**[†], and **S. M. Ling, M.D.**[§,*]

† *Division of Rheumatology, The Johns Hopkins University School of Medicine, Baltimore, MD, USA*

‡ *Laboratory of Cardiovascular Science, National Institute on Aging Intramural Research Program (NIA-IRP), Baltimore, MD, USA*

§ *Clinical Research Branch, NIA-IRP, Baltimore, MD, USA*

Summary

Objective—Osteoarthritis (OA) and vascular stiffening may share elements of common pathogenesis, but their potential relatedness has been the focus of little prior inquiry. We tested the hypothesis that these two aging-associated conditions are related to each other.

Method—We analyzed cross-sectional data from 256 participants of the Baltimore Longitudinal Study of Aging (BLSA), a study of normative aging. All underwent measurement of arterial pulse wave velocity (PWV), an index of vascular stiffness, as well as hand radiographs that were graded for evidence of OA. Twenty total joints across three joint groups (distal interphalangeal [DIP], proximal interphalangeal [PIP], carpal-metacarpal [CMC]) were each assigned a Kellgren–Lawrence grade (K–L) of 0 (normal) through 4 (severe), with K–L grades ≥2 considered evidence of definite OA. Radiographic hand OA was defined as definite OA changes in at least two of the three anatomic hand sites (DIP, PIP, CMC). OA burden was represented by the total number of affected OA joints, and a cumulative K–L grade was aggregated across all hand joint groups. The relationship of PWV with these three measures of hand OA was assessed by linear regression.

Results—Upon univariate analysis, the presence of radiographic hand OA ($\beta = 218.1$, $P < 0.01$), the total number of OA joints ($\beta = 32.9$, $P < 0.01$), and the cumulative K–L grade across all joint groups ($\beta = 12.2$, $P < 0.01$) were each associated with increased PWV. These associations, however, were no longer significant in age-adjusted models.

Conclusion—Although significant individual relationships between PWV and several measures of hand OA were observed, these associations were largely attributable to the confounding effect of age.

Keywords

Aging; Osteoarthritis; Vascular stiffness; Pulse wave velocity

Introduction

Osteoarthritis (OA) is the most common joint disorder, affecting over 12% of the US population, or nearly 21 million Americans, with a predilection for older adults[1]. OA results from progressive degeneration of articular cartilage due to wear and tear as well as

*Address correspondence and reprint requests to: Shari M. Ling, M.D., Clinical Research Branch, NIA-IRP, 5th Floor, Harbor Hospital, 3001 S. Hanover Street, Baltimore, MD 21225, USA. Tel: 1-410-350-3934; Fax: 1-410-350-3957; E-mail: lingsh@grc.nia.nih.gov.

accumulation of agents such as advanced glycation end-products (AGEs)[2,3] and denatured collagen[4]. Inflammation and free radical damage may also play a role in OA pathogenesis[5].

Interestingly, these mechanisms that contribute to OA are also important in the development of vascular stiffness, which is increasingly recognized as an independent predictor of adverse cardiovascular outcomes[6,7]. Arterial stiffness results from progressive fragmentation of elastin due to wear and tear as well as deposition of collagen in the medial layer of the walls of central arteries[8,9] and the cross-linking of these proteins to form AGEs. Recent data suggest that inflammation and free radical damage may also contribute to arterial stiffening[10]. Arterial stiffness can be quantified non-invasively by carotid-femoral pulse wave velocity (PWV).

Recently, there has been substantial interest in the relationship between various arthritic and rheumatic disorders in relation to vascular stiffness, a marker of heightened risk of cardiovascular morbidity. Indeed, a growing body of investigation has established links between arterial stiffness and lupus[11–13] as well as rheumatoid arthritis (RA)[14,15]. However, to the best of our knowledge, a direct examination of arterial stiffness in relation to OA has not been previously reported. The fact that OA and arterial stiffness are both related to the aging process suggests that these two highly prevalent disorders may share common elements in their pathogenesis. The aim of this study was to test the hypothesis that these two disorders are related to each other.

Subjects and methods

Study Population

The Baltimore Longitudinal Study of Aging (BLSA) is a multi-disciplinary normative study of aging initiated in 1958 and conducted at the National Institute on Aging in Baltimore, MD[16]. BLSA participants are community-dwelling, healthy volunteers who are predominantly Caucasian, of middle- and upper-middle-class socioeconomic status, and ranged in age from 19 to 93 years at the time of their first visit. Over 80% rated their health status as good to excellent at enrollment.

Study Sample

A total of 314 BLSA participants who had undergone an assessment of PWV and hand radiography were identified. There were 11 subjects with incomplete radiographic data, leaving 303 participants available for analysis. One additional participant with electrocardiographic evidence of myocardial infarction was also excluded. Because our primary aim was to examine the potential relatedness of vascular stiffness to OA among those without existing cardiovascular disease and whose vasoreactivity would not be affected by concomitant use of vasoactive drugs, we predominantly focused our analyses on 256 of these participants. For completeness, we also repeated the main analyses with inclusion of the 46 participants who were taking vasoactive medications, agents known to influence arterial pressure and thus PWV.

Radiographic Data

Bilateral postero-anterior (PA) hand radiographs were obtained at one or more study visits between 1984 and 1991. Radiographs were evaluated for OA in 1992–1993 by trained readers using the Kellgren–Lawrence (K–L) scale as described in the Atlas of Standard Radiographs[17]. Twenty total joints across three joint groups (10 distal interphalangeal [DIP] —including two thumb interphalangeal, eight proximal interphalangeal [PIP], and two first carpal-metacarpal [CMC] joints) were each assigned a K–L grade of 0 (normal) through 4 (severe), with K–L $\geq$2 considered evidence of definite OA at that joint[17]. The presence of OA in at least one joint at a particular joint group established the radiographic diagnosis of OA at that anatomic group. As previously reported[18], radiographic hand OA was defined as the

presence of definite OA changes in at least two of the three anatomic hand groups (DIP, PIP, CMC). We also assessed other parameters of hand OA burden, including the total number of joints with a K–L grade ≥2, and the sum of all K–L grades across the three joint groups[18, 19].

Arterial PWV

PWV was measured as described previously[20]. At least 10 arterial flow waves from the right common carotid artery and the right femoral artery were simultaneously recorded using non-directional trans-cutaneous Doppler probes (model 810A, 9–10-Mhz probes, Parks Medical Electronics, Inc., Aloha, OR). The foot of the flow (the point of systolic flow onset) was identified by a custom-designed computer algorithm and verified or manually adjusted by the reader after visual review. The time differential between the nadir of simultaneously recorded carotid and femoral flow waves was then measured. The distance traveled by the flow wave was measured using an external tape measure over the body surface and was calculated as the distance from the right carotid measuring site to the manubrium added to the distance from the manubrium to the right femoral measuring site. PWV was calculated as the distance traveled by the flow wave divided by the transit time. PWV measures were obtained as contemporaneously as possible to the radiographs. Overall, the mean time interval between the PWV measurements and the radiographic ascertainment of OA status was 7.9 years (SD = 4.7 years).

Anthropometric and Hemodynamic Measurements

Blood pressure measurements were recorded in the morning after participants had consumed a light breakfast and assumed a seated position following a five-minute quiet rest period. Measurements were made in both arms with a mercury sphygmomanometer using an appropriately sized cuff. Values used in this study were the average of the second and third measurements taken from both the right and left arms. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) values were defined by Kortokoff phases I and V, respectively. Body mass index (BMI) was calculated as body weight (kg) divided by height^2 (m^2). Blood samples were drawn from an antecubital vein between 7 and 8 AM after an overnight fast to assess lipid profiles. Participants were not allowed to smoke, engage in significant physical activity, or take medications prior to blood collection. The concentrations of plasma triglycerides and total cholesterol were determined by an enzymatic method (Abbott Laboratories, ABA-200 ATC Biochromatic Analyzer, Irving, TX). The concentration of high-density lipoprotein (HDL)-cholesterol was determined by a dextran sulfate-magnesium precipitation procedure[21]. Low-density lipoprotein (LDL)-cholesterol concentrations were estimated by the Friedewald formula. Diabetes and smoking status were obtained by self-report. Smokers were further categorized as those with a past or current history of smoking.

Statistical Analysis

The association of demographic and clinical variables among participants with and without radiographic hand OA was analyzed by Student's *t* testing for normally distributed variables and Wilcoxon rank sum testing for nonparametric variables. Correlations of arterial stiffness with radiographic hand OA, cumulative K–L grade, and the total number of OA joints were made using the nonparametric Spearman rank test. The relationship between PWV and radiographic hand OA was first assessed by univariate linear regression. In addition, the relationship of PWV with the other measures of OA burden, namely the total K–L grade and the total number of OA joints, was also assessed by univariate linear regression. Next, the independent relationship of PWV with OA was further examined using multivariate analysis, with adjustment for age and other clinical variables, including BMI, sex, SBP and DBP, smoking and diabetes status.

Given the unequal age distribution of those with and without hand OA, we performed a propensity score analysis which adjusted for baseline differences in age between the two groups. This analysis, performed using logistic regression, adjusted for age, BMI, SBP, DBP, PWV, serum cholesterol, serum triglycerides, and diabetes. We also performed a stratified analysis of those participants over 55 years of age, the minimum age of all those with hand OA. Statistical significance was defined as an alpha level less than 0.05 using a two-tailed test. Statistical analysis was performed using the STATA software package (Version 8.0, College Station, TX) and SAS (Version 8.1, Cary, NC).

Results

Complete data were available on 256 participants, 52 of whom had radiographic hand OA. Characteristics of the study participants are shown in Table I. Participants with hand OA were on average 24 years older ($P < 0.0001$) than those without hand OA. Men and women were approximately equally represented in the two groups. Compared to those without hand OA, participants with hand OA had higher mean BMI (24.6 kg/m^2 vs. 23.8 kg/m^2, $P = 0.048$) and were more likely to be diabetic (5.8% vs. 0.9%, $P = 0.026$). Participants with hand OA also had higher mean HDL (52 mg/dl vs. 46 mg/dl, $P = 0.037$), higher mean total cholesterol (223 mg/dl vs. 205 mg/dl, $P = 0.01$), and higher mean SBP (134 mmHg vs. 123 mmHg, $P = 0.0001$).

In addition, participants with radiographic hand OA averaged 6.7 joints (range 2–15) with a K–L grade of 2 or higher and had a mean total K–L grade of 19.9 (range 5–49). PWV for this group ranged from 323.7 cm/s to 1861.1 cm/s with a mean of 720.6 cm/s (SD = 262). When stratified by hand OA status, mean PWV was 894.4 cm/s (SD = 277.6) in those with hand OA, and 676.3 cm/s (SD = 239.1) in those without hand OA ($P < 0.0001$).

The relationships of mean PWV with radiographic hand OA, total number of OA joints, and cumulative K–L grade were first assessed by Spearman rank correlation. The correlation coefficients for each of these comparisons exceeded 0.3, indicating good correlation. (PWV with radiographic hand OA = 0.36 ($P < 0.0001$), with the total number of OA joints = 0.43 ($P < 0.0001$) and with cumulative K–L grade = 0.48 ($P < 0.0001$).)

Results of univariate linear regression are presented in Table II. The presence of radiographic hand OA was associated with an increase of 218.1 cm/s in mean PWV ($P < 0.0001$). The other two measures of OA burden—the total number of OA joints and the cumulative K–L grade, both modeled as continuous variables—were each similarly associated with significant increases in mean PWV (32.9 cm/s and 12.2 cm/s, respectively, $P < 0.0001$) as well.

Adjusted analysis was then performed to examine the potential confounding effect of several demographic and clinical variables. The age-adjusted analysis showed a marked diminution in the strength of the association of PWV and radiographic hand OA ($\beta = -2.7$, $P = 0.95$) (Table II). Comparable results were observed for the associations between PWV and the total number of OA joints ($\beta = 0.004$, $P = 0.99$) as well as the cumulative K–L grade ($\beta = 0.4$, $P = 0.86$). The relationship between PWV and radiographic hand OA remained non-statistically significant on further adjustment for other potential confounders, including BMI, sex, smoking status, SBP, DBP, and diabetes status (Table II). These results were not altered with the inclusion of the inflammatory markers, erythrocyte sedimentation rate (ESR) and white blood cell count (WBC) in the regression models (data not shown).

Given the substantially different distributions of age between the OA and non-OA groups, we repeated the analysis using propensity scoring, which adjusts for baseline differences between groups, thereby making them more comparable. This method yielded the same result—the association between PWV and radiographic hand OA was found to be non-statistically significant ($\beta = -23.1$, $P = 0.6$). In light of the difference in age distribution between those

participants with and without hand OA, we further restricted the analysis to those exceeding the minimum age for hand OA in this study, namely participants 55 years of age and older. This subset consisted of 105 subjects, 51 of whom had radiographic hand OA while 54 did not. The mean age of these two groups was 67.6 years (SD = 8.6 years) and 63.6 years (SD = 7.7 years), respectively. The presence of radiographic hand OA was associated with a 40.0 cm/s increase in PWV, but this did not achieve statistical significance ($P = 0.73$). When adjusting for age, the strength of the association was no longer observed (β coefficient = −10.3, $P = 0.85$).

Finally, because of concern that excluding patients who were taking vasoactive medications may have introduced unintended bias, we repeated the main analyses after inclusion of the 46 participants on vasoactive agents. In this analysis, mean PWV was higher still, at 270.7 cm/s, in those with hand OA compared to those without hand OA. A similar pattern then emerged with adjustment, whereby mean PWV was substantially reduced to 16.7 cm/s with age-adjustment (non-statistically significant, $P = 0.7$), and to 39.3 cm/s with multivariate analysis ($P = 0.4$), which contained the other pertinent variables.

Discussion

This report addressed the potential relationship between increased vascular stiffness and hand OA, an area rarely studied. This study examined the hypothesis that increased vascular stiffness is associated with hand OA. We found that vascular stiffness as measured by PWV was in fact related to the presence and burden of radiographic hand OA. Furthermore, this relationship was observed using three widely accepted measures of hand OA. This relationship was found to be largely explained by adjustment for age.

OA and increased arterial stiffness are strongly related to aging, making them increasingly important health care concerns as life expectancies continue to rise and the global population ages. A number of studies have found associations of excess cardiovascular morbidity and mortality in individuals with OA. For example, Cerhan *et al.* showed overall cardiovascular mortality to be directly proportional to the extent of radiographic evidence of OA[22]. They specifically demonstrated diminished survival in women with an increased number of joint groups affected by OA. Similarly, in a Finnish cohort Haara *et al.* demonstrated that the presence of advanced thumb carpo-metacarpal OA in men predicted a 32% increased risk of total mortality[23]. Recent investigations of the biology of OA and of arterial stiffness have uncovered elements of similar pathophysiology, making attractive the hypothesis that these two conditions may be causally linked rather than merely independent features of aging. Among the most widespread theories of primary OA pathogenesis is that the disease is a consequence of cumulative “wear and tear” on cartilage[24]. Like OA, arterial stiffening traditionally has been attributed to the “wear and tear” that results from the repeated cycles of vascular distension and recoil, which lead to fragmentation of elastin fibers and subsequent deposition of collagen in the medial wall of elastic arteries[8,25].

The phenomenon of accumulation of glycation end-products in cartilage may be particularly relevant to our hypothesis. Non-enzymatic glycation is a common process of post-translational protein modification involving covalent bonding between amino acids and reduced sugars, followed by a series of chemical reactions that ultimately generate AGEs. AGEs accumulate with advancing age, particularly in human cartilage[2], and they adversely affect cartilage metabolism and mechanical properties, compromising matrix integrity[26]. Over time, arteries are repeatedly exposed to the effects of AGEs, which leads to covalent cross-linking of adjacent collagen fibrils in the medial layer of the walls. This, in turn, markedly increases the tensile strength of these fibrils and, hence, the stiffness of the arterial wall[27].

It is noteworthy that vascular stiffness has been associated with a number of other rheumatic diseases, including lupus[11–13] and RA[14,15], with chronic inflammation being the presumed common pathophysiologic link. Although OA is generally considered a degenerative rather than inflammatory arthropathy, recent evidence suggests inflammatory processes may play a role in its pathogenesis[5]. Analogously, newer data suggest that inflammation may play a direct role in mediating arterial stiffness[10]. Reactive oxygen species constitute another category of compounds that exert effects on both cartilage and the vasculature. Free radical species have been implicated in cartilage degeneration and OA pathogenesis, for example, by causing chondrocyte lipid peroxidation, a reaction that has been directly linked to collagen oxidation and degradation. Similarly, oxidative stress has been shown to promote vascular disease[28], and experimental evidence has demonstrated that reducing oxidative stress may reduce aortic stiffness[29].

We acknowledge the following limitations. Our study population primarily consisted of affluent Caucasian volunteers, a highly selected group that may not be representative of the general population. In addition, by focusing exclusively on hand joints, we may not have adequately accounted for the full clinical burden of OA disease throughout the human body. Moreover, our assessment of vascular stiffening by PWV only reflects central arterial stiffness. We did not assess the potential association between OA and properties of more distal arteries, for example, by measuring distal compliance, a correlate of microvascular stiffness that may reflect early vascular disease. We also note that PWV and OA were often measured at different visits. This was primarily a consequence of too few participants who presented at any given time to undergo simultaneous evaluation of both OA and PWV status on the same visit. Though the main analyses were conducted among 256 participants, it remains possible that our study lacked statistical power. Despite these limitations, the exceptional richness of the BLSA cohort made it uniquely suited to examining the hypothesis of an association between OA and vascular stiffness.

This study uniquely highlights the association of hand OA and vascular stiffening, a surrogate marker of cardiovascular disease risk. This relationship has been largely unaddressed in the literature. In fact, an association between hand OA and vascular stiffening was identified, in that those with hand OA compared to those without hand OA had substantially higher degrees of vascular stiffness. However, this association was principally attributed to confounding by age. The use of accepted and well validated measures of hand OA and state-of-the art techniques to assess arterial stiffening also facilitated this study, whose results raise a number of questions and will hopefully spur further investigation. Moreover, in light of the pathogenetic factors common to both of these disorders and the differing age distributions of the OA and non-OA groups in our study population, these findings call for further analysis in a larger cohort or in age-matched case–control studies.

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Table I

Characteristics of study participants with and without hand OA

Participant characteristics	No radiographic hand OA (*n* = 204)	Radiographic hand OA (*n* = 52)	*P*-value
Age (years)	43.2 (14.8)	67.2 (8.9)	<0.0001
Male sex* (%)	109 (53.4)	25 (48.1)	0.49
Smoking* (%)	70 (34.4)	18 (34.6)	0.96
BMI (kg/m^2)	23.8 (3.6)	24.6 (2.9)	0.048
Diabetes* (%)	2 (0.9)	3 (5.8)	0.026
LDL (mg/dl)	112 (31)	120 (33)	0.099
HDL (mg/dl)	46 (12)	52 (16)	0.037
Cholesterol (mg/dl)	205 (34)	223 (35)	0.001
Triglycerides (mg/dl)	94 (57)	112 (103)	0.12
SBP (mmHg)	123 (18)	134 (18)	0.0001
DBP (mmHg)	79 (10)	79 (9)	0.79

Values are expressed as means (±standard deviation) unless otherwise noted. Smoking indicates current or former smoker.

*Denotes frequency.

Table II

Univariate, age-adjusted, and multivariate analysis of PWV and radiographic hand OA, number of OA joints, and cumulative K–L grade

	Unadjusted			Age-adjusted			Multivariate*		
	β Coeff	95% CI	*P*-value	*β* Coeff	95% CI	*P*-value	*β* Coeff	95% CI	*P*-value
Radiographic hand OA	218.1	142.5–293.8	<0.0001	−2.7	−82.1 to 76.6	0.95	9.2	−64.2–82.5	0.81
No. of OA joints	32.9	23.4–42.6	<0.0001	0.004	−11.2 to 11.2	0.99	5.6	−5.0–16.2	0.30
Cumulative K–L grade	12.2	8.9–15.4	<0.0001	0.4	−3.7 to 4.5	0.86	2.9	1.0–6.7	0.14

*The multivariate model incorporates age, BMI, sex, SBP, DBP, smoking, and diabetes status.