Knee Osteoarthritis and Risk of Hypertension:

A longitudinal cohort study

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ABSTRACT

Whilst previous research has indicated an association between osteoarthritis and cardiovascular disease, it remains unclear whether people with osteoarthritis are at greater risk of developing hypertension. The aim of this study was to answer this uncertainity. We used the data of the Osteoarhritis Iniative, an ongoing public and private longitudinal study including people at higher risk of osteoarthritis or having knee osteoarthritis. Knee osteoarthritis was defined through radiological and clinical assessment. Incident hypertension was defined as a systolic blood pressure $\geq$140 mmHg and/or a diastolic value $\geq$90 mmHg. Multivariate Cox's regression analyses were constructed where the presence of knee osteoarthritis as the exposure and incident hypertension as the outcome during a 96 month follow-up interval. A total of 3,558 people with normative blood pressure values at baseline were analyzed (1,930 OA / 1,628 controls). Incidence of hypertension within the follow-up interval was significantly higher in people with knee osteoarthritis compared to those without (60/ vs. 55/1,000 persons/years; $p<0.0001$). After adjusting for 13 confounders, people with knee osteoarthritis had a 13% higher chance of developing hypertension (Hazard ratio = 1.13; 95%CI: 1.01-1.26, $p=0.03$). Propensity score analysis did not alter these conclusions. In conclusion, this is the first longitudinal data analysis to demonstrate that people with knee osteoarthritis have a higher chance of developing hypertension compared to those without osteoarthritis. Our data suggests that monitoring blood pressure and prescribing health promotion interventions may be warranted among people with osteoarthritis to mitigate the potential onset and adverse consequences of hypertension.

INTRODUCTION

Osteoarthritis is one of the most common chronic musculoskeletal diseases worldwide. [1,2] It has a high prevalence, estimated to be 10% in men and 20% in women over the age of 60 years. [3] Previous research has demonstrated that people with osteoarthritis have a higher prevalence of cardiovascular diseases (CVD), as reported by a recent meta-analysis including more than one million participants. [4] People with osteoarthritis have a number of risk factors for CVD, such as low levels of physical activity, [5] high levels of depressive and anxiety symptoms, [6] and metabolic abnormalities, such as diabetes and metabolic syndrome. [7] Whilst cross-sectional data suggests increased prevalence of CVD in those with osteoarthritis, [4] considerably less is known about the incidence of CVD. Some recent studies have suggested that people with osteoarthritis may be at increased risk of developing CVD, although with no univocal results. [8–10] This is concerning since CVD is a leading cause of global mortality, particularly in the Western world. [11] Furthermore people with osteoarthritis may be at increased risk of premature death due to CVD. [12]

The heightened risk of CVD among people with osteoarthrits has been hypothesized to be increased and potentially influenced through various mechanisms. Firstly, osteoarthritis is often characterized by some degree of low-grade inflammation which is also a potential CVD risk factor. [13] Secondly, osteoarthritis is characterized by relevant modifications of extra-cellular matrix (ECM) [14] which may also increase the risk of CVD. [15] Finally, pain and disability associated with osteoarthritis may result in physical inactivity, which, over time, may subsequently led to CVD. [16]

Whilst a significant number of cross-sectional studies have reported the association between osteoarthritis and hypertension [17–24], no longitudinal studies have to the best of our knowledge examined the incidence of hypertension in this population. This is an important omission given that it remains unclear whether there is a causal relationship between osteoarthritis and hypertension which may provide further insights into its pathophysiology for those with osteoarthritis. Whilst

longitudinal research cannot infer causality, it can enable some clarification of the directionality of the cross-sectional relationships observed. Moreover, such analyses would also provide greater insight into the magnitude of this comorbidity within this population, which has clinical relevance for preventing the sequalae of hypertension such as stroke and CVD. [25] It may also identify appropriate targeted interventions to prevent hypertension in people with osteoarthritis if a relationship were observed.

Given this, the purpose of this study was to determine whether people with knee osteoarthritis have an increased chance of developing hypertension over an eight-year follow-up period, compared to people without knee osteoarthritis.

METHODS

Data source and subjects

All participants in this study were recruited as part of the ongoing, publicly and privately-funded, multicenter Osteoarthritis Initiative (OAI) study, which is available for public access (http://www.oai.ucsf.edu/). Patients were recruited from four clinical sites in the US (Baltimore, MD; Pittsburgh, PA; Pawtucket, RI; and Columbus, OH) between February 2004 and May 2006.

The OAI study protocol was approved by the institutional review board of the OAI Coordinating Center, University of California at San Francisco. Specific datasets used were those recorded during baseline and screening evaluations (November 2008) and those evaluating the participants until the last evaluation (after 96 months from baseline evaluation).

Cases

The osteoarthritis cohort was the 'cases' and were defined as: i) having knee osteoarthritis and reported knee pain in a 30-day period in the past 12 months; or ii) at high risk of developing knee osteoarthritis at baseline (e.g. overweight/obese, knee injury/operation, parents/siblings with total knee replacement, frequent knee-bending activities that increase risk, and hand/hip osteoarthritis). All participants provided written informed consent. Knee osteoarthritis was defined as the combination in the clinical reporting and assessment of pain and stiffness (i.e. pain, aching or stiffness in or around the knee on most days during the last year), and radiographical evidence of osteoarthritis on the baseline fixed-flexion radiograph defined as the presence of tibiofemoral osteophytes (correspondent to Osteoarthritis Research Society International atlas grades 1-3, clinical center reading; [26]). In the OAI, the presence of pain, stiffness, and physical functioning (or disability) due to OA was assessed through the WOMAC (Western Ontario and McMaster Universities Arthritis Index).[27] Briefly, the responses for each subscale (pain, stiffness, disability) are categorized on a five-point Likert scale ranging from none (0 points) to extreme (4 points). The maximum possible

score is 68, and the final score was normalized to 100 (range 0–100), with higher scores reflecting greater activity limitations. [27]

Outcomes

The assessment of blood pressure was made through a single measurement performed by a trained nurse at the right arm, unless contraindicated. Hypertension was defined as a value of systolic blood pressure $\geq$ 140 and/or diastolic blood pressure $\geq$ 90 mmHg in agreement with the guidelines suggested for this condition. [28] In the OAI dataset, blood pressure was recorded at baseline and follow-up points of 12, 24, 36, 48, 72 and 96 months. Incident hypertension was defined as a normal blood pressure measurement at baseline but a measurement reaching the hypertensive threshold within a subsequent follow-up interval.

Covariates

Several candidate explanatory variables were identified to explore the possible association between osteoarthritis and incident hypertension. These included: race ("whites" vs. others); smoking habits ("previous/current" vs. never); educational level ("degree" vs. others); yearly income (missing data, < or $\geq$ $50,000); body mass index (BMI) measured by a trained nurse with a cut-off of more/equal than 30 Kg/m^2 for defining obesity; and medical co-morbidities were assessed through the modified Charlson Comorbidity Index (CCI), where higher scores indicate an greater number of morbidities and poorer health [29]; physical activity was evaluated through the validated Physical Activity Scale for the Elderly [30]. The scale covers 12 different activities, such as walking, sports, and housework, and is scored from 0 without a maximum score; and any depressive symptoms was derived from the 20-item Center for Epidemiologic Studies-Depression (CES-D) instrument [31]. The range of possible values for scale scores is 0–60, with the higher scores indicating more depressive symptoms [31]. Specifically the diagnosis of diabetes, chronic obstructive pulmonary disease (COPD), cancer or cardiovascular disease (i.e. the presence of heart failure, heart attack, peripheral artery disease, and/

or stroke) were reported descriptvetly in our analyses. Finally, also the use of non-steroidal anti-inflammatory drugs (NSAIDs) (prescribed or not by a doctor) was included as potential confounder.

Statistical analyses

For continuous variables, data normality was assessed and confirmed using the Kolmogorov-Smirnov test. Data were presented as mean and standard deviation (SD) values for quantitative measures, and frequency and percentages for discrete variables by knee osteoarthritis presence. P-values were calculated for continuous variables using the independent Student T-test and for categorical parameters the chi-square test between people with knee osteoarthritis compared to those without.

The incidence of cases who developed hypertension within the follow-up period was calculated as the number of new cases per 1000 person-years during the follow-up. Multivariate Cox's regression analyses were constructed using the presence of knee osteoarthritis as the exposure and incident hypertension during the follow-up period as the outcome. The multivariate model included all confounding factors that were significantly different between participants with and without knee osteoarthritis at baseline or were significantly associated with incident hypertension at follow-up (denoted as p-value <0.05 for both selections). Multi-collinearity among covariates was assessed through variance inflation factor (VIF), taking a cut-off of two as reason for exclusion. No variable was excluded for this reason. The basic model was not adjusted for any confounders, whilst the fully adjusted model adjusted for baseline values of: age; gender; race; BMI; education; smoking habits; yearly income; CCI; baseline PASE score; baseline CESD score; use of NSAIDs; and baseline values of systolic and diastolic BP. In a sensitivity analysis, to better control the role of possible confounding effects on the association between knee osteoarthritis and incident hypertension, the propensity score matching methodology was applied.[32] Data of Cox's regression analyses were reported as hazard ratios (HRs) with 95% confidence intervals (CIs).

Several sensitivity analyses were conducted evaluating the interaction between the presence of knee osteoarthritis and selected factors (e.g. age below or more than 65 years, obesity, presence of any disease, yearly income, gender, race, education, smoking habits, yearly income and presence/absence of diabetes and CVD at baseline) in predicting hypertension at follow-up, although no factor was significant.

All analyses were performed using the SPSS 21.0 for Windows (SPSS Inc., Chicago, Illinois). All statistical tests were two-tailed and statistical significance was assumed for a p-value <0.05.

RESULTS

Study participants

Among 4,796 potentially eligible individuals, 1,005 were excluded due to pre-existing hypertension at the baseline assessment, 33 were excluded as there was insufficient information to confirm a diagnosis of knee osteoarthritis and 200 were lost at follow-up. Accordingly, 3,558 participants were eligible for this study (**Figure 1)**.

Baseline analyses

The 3,558 participants (1,439 males/2,119 females) had a mean age of 60.4±9.0 years (range: 45-79). At baseline, 1,930 people with knee osteoarthritis were compared to 1,628 participants without knee osteoarthritis.

The baseline characteristics of the knee osteoarthritis and non-osteoarthritis participants (i.e. participants at higher risk of knee osteoarthritis) are reported in **Table 1**. The osteoarthritis participants were more frequently older (61.8±9.1 versus 58.9±8.8 years) than those without osteoarthritis ($p<0.0001$), whilst no significant differences emerged in terms of gender and race. Individuals with knee osteoarthritis had significantly higher BMI values, had a higher educational level and income, and they were less active compared to the non-osteoarthritis group (**Table 1**). Regarding medical conditions, participants with osteoarthritis more frequently reported diabetes and had a higher CCI (**Table 1**). Finally, participants with knee osteoarthritis showed significantly higher systolic blood pressure (119.4±10.8 versus 117.1±11.3 mmHg, $p<0.0001$) and diastolic blood pressure (73.4±8.1 versus 72.7±8.6 mmHg, $p=0.02$) values at baseline compared to without osteoarthritis. No significant differences emerged in terms of the use of NSAIDs between individuals with knee OA and the controls ($p=0.06$).

Follow-up analyses

After a 96 month follow-up, 1,428 individuals (40.2% of the baseline population) developed hypertension, with an incidence of 57 cases (95% CI: 23-85) per 1,000 person-years. The incidence of newly diagnosed hypertension was significantly higher in people with knee osteoarthritis at baseline (60 per 1,000 person-years; 95% CI: 37 to 85) compared to those without (55 per 1,000 person-years; 95% CI 23 to 89) ($p<0.0001$) as reported in **Figure 2**.

Figure 3 shows the means of systolic (left panel) and diastolic (right panel) blood pressure by presence of knee osteoarthritis at the baseline during the follow-up period. The presence of knee osteoarthritis at the baseline was associated with higher blood pressure mean values for systolic ($p=0.04$), but not for diastolic blood pressure ($p=0.97$).

On multivariate analysis, significant predictors of incident hypertension were: knee osteoarthritis which increased the chances of incident hypertension by 13% (HR=1.13; 95% CI: 1.01 to 1.26, $p=0.03$), age (for each year, HR=1.02; 95% CI: 1.001 to 1.02, $p<0.01$), female gender (HR=1.15; 95% CI: 1.03 to 1.28, $p=0.02$), non-white ethnicity (HR=1.53; 95% CI: 1.34 to 1.75, $p<0.01$), BMI (one point corresponded to an increase in incident hypertension of 2% HR: 1.02; 95% CI: 1.01 to 1.03; $p=0.002$), and systolic blood pressure at the baseline (each mmHg increases the risk of hypertension at follow-up of 4%; HR=1.04; 95% CI: 1.03 to 1.05, $p<0.01$). Using a propensity score the association between knee osteoarthritis at the baseline and incident hypertension remained evident (HR=1.11; 95% CI: 1.01 to 1.24; $p=0.05$).

DISCUSSION

In this large prospective study, our data suggests that the presence of knee osteoarthritis is associated with a small but significant increased chance of developing hypertension over an 8-year follow-up. Specifically, after adjusting for potential confounders (including baseline blood pressure values at the baseline), knee osteoarthritis was associated with a 13% greater chance of developing hypertension.

In this cohort, knee osteoarthritis was a significant predictor for developing hypertension at follow-up. Several mechanisms have been suggested to explain this possible association. [33] Firstly, people with knee osteoarthritis without hypertension at baseline may already have pathological modifications of ECM leading to reduced blood vessel elasticity of blood vessels and consequently to hypertension. These hypotheses are partially confirmed by our finding since the higher incidence of hypertension observed in people with knee osteoarthritis at baseline seems to be attributable to higher systolic blood pressure values than diastolic, where it is known that systolic blood pressure is more dependent on ECM changes than diastolic one. [34] Molecules such as disintegrin and metalloproteinase involved in ECM remodeling appear to have a role in the development of hypertension. [33] Interestingly, as shown by our survival curves, people with knee OA at baseline developed hypertension mostly at the end of the follow-up. Even if we don't exactly know the reasons, we can assume that the pathways mentioned before need time for altering the ECM and so leading to hypertension. However, other studies are needed in this sense. Thirdly, although osteoarthritis is not considered an inflammatory arthritis, people with osteoarthritis frequently present with a low-chronic inflammation grade [35,36] that could a role in the development of CVD and hypertension. [37] Finally, although adjusted for potential confounders, the conditions in common between osteoarthritis and hypertension (such as age, obesity, diabetes, reduced physical activity) may be additional explanatory factors. Of particular note is that people with OA usually report lower levels of physical activity and are more sedentary that those without [38] and these factors probably play a relevant role in the development of hypertension.[39] However, using the propensity score and the analyses

adjusted for these potential confounders, our findings did not significantly change, indicating that the role of these baseline confounders is probably marginal.

Previous studies investigating the role of osteoarthritis as potential CVD risk factor, reported that people with osteoarthritis had a significant higher prevalence of hypertension. [4,8–10] However, the nature of these studies did not allow the directionality of this association. We attempted to address this limitation in the literature in this study. The data proposes that people with osteoarthritis had a higher risk of developing hypertension at the follow-up, indicating that blood pressure should be strictly monitored in these subjects. Of note, almost half of the people with knee osteoarthritis at the baseline assessment developed hypertension, suggesting the importance of this condition. Improved surveillance and management of this condition can have a significant impact on long-term health and prevention of diseases such as stroke and cardiovascular disease.

Our findings should be considered within the limitations of our study. The measurement of blood pressure was made on one occasion with insufficient data to determine whether some individuals had blood pressure controlled through medications. The findings of this study therefore related to new-onset hypertension or uncontrolled hypertension with or without drug treatment. Second, the diagnosis of co-morbidities was self-reported and not verified through a review of the participant's medical notes. Third, we do not have sufficient information regarding the use of blood pressure lowering medications which could introduce bias in our findings. It is in fact possible that people having normal blood pressure at the baseline is due to the use of medications and vice versa. Finally, we did not assess any inflammatory or ECM marker, although inflammation could be associated with higher CVD risk.[40] Nonetheless, allowing for these caveats, our study involves a large population over a long follow-up period. Moreover, we adjusted our analyses for multiple important confounders.

In conclusion, our study demonstrated that people with knee osteoarthritis have a greater risk of developing hypertension in people with osteoarthritis over an 8-year period. Since some interventions aiming to improve osteoarthritis symptoms (e.g. increasing physical activity and weight loss reduction) seem to be effective from a cardiac perspective, further studies are needed to better understand if to treat osteoarthritis can decrease hypertensive risk in these individuals.

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Table 1. Baseline characteristics classified according to presence or not of knee osteoarthritis (osteoarthritis).

Numbers are mean values (and standard deviations) or number (and percentages), as appropriate.

Variable	Knee osteoarthritis (n=1,930)	No osteoarthritis (n=1,628)	*p* value*
Age (years)	61.8 (9.1)	58.9 (8.8)	<0.0001
Females (n, %)	1125 (58.3)	993 (61.0)	0.11
White race (n, %)	1574 (81.6)	1340 (82.5)	0.48
BMI (kg/m^2)	29.2 (4.8)	27.1 (4.5)	<0.0001
Smoking (previous/current) (n, %)	732 (45.4)	878 (46.0)	0.73
College and above (n, %)	598 (36.9)	552 (28.8)	<0.0001
Yearly income (<50,000 $)	719 (37.3)	504 (31.0)	<0.0001
PASE score (points)	158.4 (80.7)	170.0 (84.0)	<0.0001
Medical conditions			
Diabetes (n, %)	167 (8.8)	78 (4.9)	<0.0001
COPD (n, %)	38 (2.0)	34 (2.1)	0.81
Cardiovascular diseases (n, %)	131 (7.0)	88 (5.5)	0.08
Cancer (n, %)	101 (5.2)	72 (4.4)	0.27
Charlson co-morbidity score (points)	0.4 (0.9)	0.3 (0.8)	0.01
CESD (points)	6.4 (6.7)	6.5 (6.5)	0.93
Systolic blood pressure (mmHg)	119.4 (10.8)	117.1 (11.3)	<0.0001
Diastolic blood pressure (mmHg)	73.4 (8.1)	72.7 (8.6)	0.02

*****Unless otherwise specified, *p values* are calculated with an independent Student T-test for continuous and with a chi-square test for categorical variables, respectively.

Abbreviations: BMI: body mass index; COPD: chronic obstructive pulmonary disease.; CESD: Center for Epidemiologic Studies-Depression; PASE: physical activity scale for the elderly.

Figure 1. Cohort flow-chart.

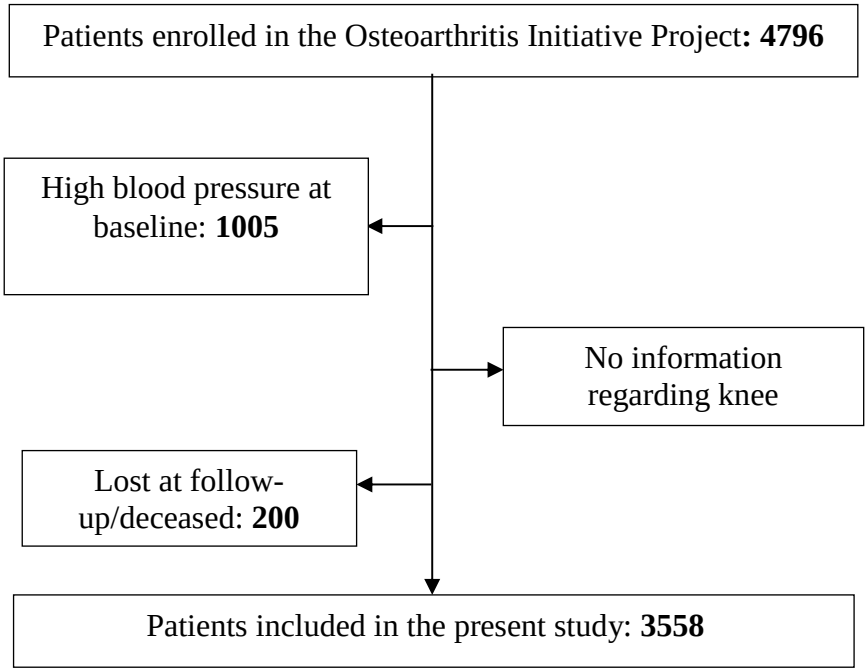


Figure 2. Risk of hypertension by presence of knee osteoarthritis at the baseline.

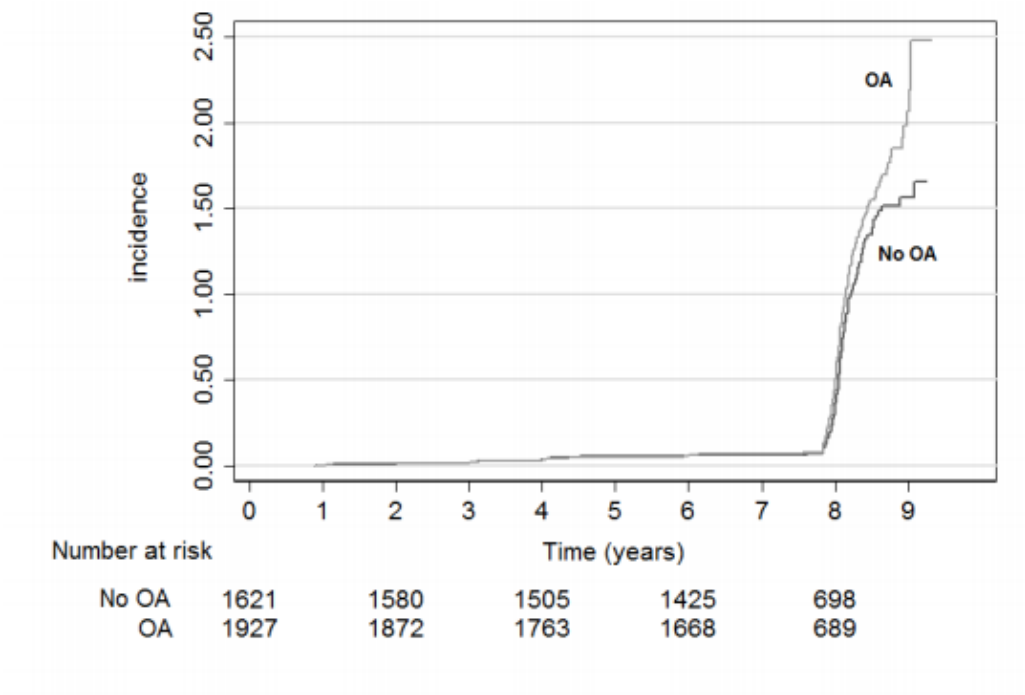
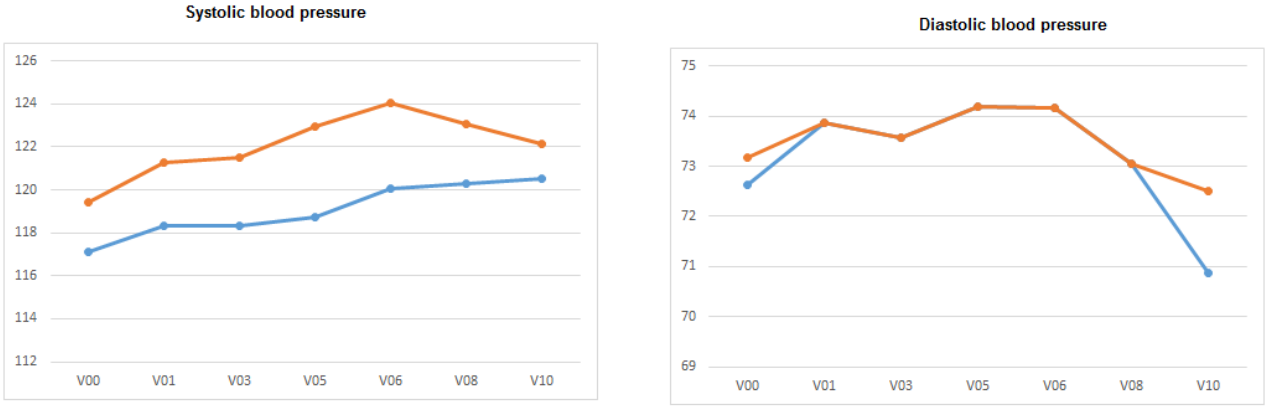


Figure 3. Mean systolic (left) and diastolic (right) blood pressure values by the presence of knee osteoarthritis at the baseline.



Notes: the red line represent the people having knee osteoarthritis at the baseline; the blue those without.