Mortality in osteoarthritis patients

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Objectives: To investigate whether all-cause mortality and deaths due to cardiovascular disease are increased in patients who have consulted primary or secondary health care with symptoms and signs of osteoarthritis (OA).

Method: This study included 383 patients with symptomatic OA at multiple sites from the Genetics ARthrosis and Progression (GARP) study (mean age 60 years, 82% women, 3693 person-years of follow-up) and 459 patients with primary hand, knee, or hip OA from the Osteoarthritis Care Clinic (OCC) study (mean age 61 years, 88% women, 1890 person-years of follow-up). Standardized mortality ratios (SMRs) with 95% confidence intervals (CIs) were calculated for all-cause mortality and causes of deaths in comparison to the general population. Cox proportional hazard ratios (HRs) with 95% CIs were used to associate baseline characteristics with all-cause mortality.

Results: In the GARP study, 26 patients died whereas 48 deaths were expected (SMR 0.54, 95% CI 0.37–0.79). The SMR was 0.47 (95% CI 0.29–0.76) in women and 0.73 (95% CI 0.39–1.35) in men. Similar results were found in the OCC study (SMR 0.45, 95% CI 0.25–0.82). Malignancy and cardiovascular disease were the main causes of deaths in GARP. Male sex (HR 3.04, 95% CI 1.38–6.69), increasing age (HR 1.10, 95% CI 1.05–1.16), and self-reported cancer (HR 8.29, 95% CI 3.12–22.03) were associated with increased mortality in GARP.

Conclusions: Patients consulting health care for their OA are not at higher risk of death than the general population. These results suggest that the management of OA patients may not need to focus specifically on the treatment of cardiovascular risk factors and comorbidities.

Osteoarthritis (OA) is a common disease with rising prevalence. Recently, increased all-cause mortality was found among subjects surveyed from the general population with hip and knee pain and radiographic signs of OA (1). Besides atherosclerosis, diabetes, walking disability, and use of non-steroidal anti-inflammatory drugs (NSAIDs) may explain a possible association between OA and mortality (1, 2). For clinical practice this could mean that management of patients with OA should focus on effective treatment of cardiovascular risk factors and comorbidities (1, 3). In this study we aimed to investigate whether OA patients who present themselves in health care with OA experience an increased mortality and whether this is due to cardiovascular causes.

Method

Study design

We investigated two prospective observational cohorts of OA patients. The Genetics ARthrosis and Progression (GARP) cohort comprised 192 Caucasian sibling pairs (384 patients) with symptomatic primary OA (diagnosed by rheumatologists, orthopaedic surgeons, and general practitioners) at multiple sites in the hand or in at least two of the following sites: hand, knee, hip, or spine (4). These patients were included in the study between August 2000 and March 2003, after informed consent had been obtained. Twenty patients with shortened life expectancy were excluded: Eleven aged 75 years and older at the time of inclusion and nine with poor health. The study was approved by the medical ethics committee.

The Osteoarthritis Care Clinic (OCC) cohort consisted of 460 consecutive patients who were diagnosed by a rheumatologist with primary hand, knee, or hip OA and referred to a clinical nurse specialist for education between August 2005 and April 2009 (5).

Demographics and clinical characteristics

Demographic characteristics, smoking status, and comorbidities (verified by a physician) were collected by standardized questionnaires. Self-reported pain and functional limitations were assessed by subscales of the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) for knees and hips, and the Australian/
Canadian (AUSCAN) Osteoarthritis Hand Index for hands. WOMAC subscales, with a visual analogue scale (VAS) format (range 0–100, higher scores = worse outcome), were available for 383 GARP patients. A Likert scale (0 = none to 4 = extreme) was used for the AUSCAN subscales pain (range 0–20) and function (range 0–36) in 351 GARP and all OCC patients.

Follow-up and assessment of mortality

Observation time started on the date of inclusion and ended on either 2 November 2011, the date of death, emigration, or loss to follow-up, whichever occurred first (complete follow-up for 98% of the cohort). Person-years were counted for all participants.

Vital status was verified by using municipal registries (Gemeentelijke Basis Administratie) and primary causes of death of GARP patients by the Central Bureau of Statistics (CBS), the national repository for death certificates. These data were compared with causes of deaths (ICD-10 classification codes) in the general population.

Data analysis

Standardized mortality ratios (SMRs) with 95% confidence intervals (CIs) were calculated for all-cause mortality and cause-specific mortality, using STATA version 10.1 (Statacorp, College Station, TX, USA). For expected numbers of deaths from age- and sex-specific mortality data for the general population, we used the middle of the follow-up time as the reference year.

‘Healthy cohort’ effects may occur because of exclusion of patients with a shortened lifespan. As this effect ebbs away after a few years, enabling unbiased analyses (6), SMRs were also calculated by delaying the start of follow-up.

Associations between characteristics of patients at baseline and all-cause mortality in GARP were studied using univariate and multivariate Cox proportional hazards models, adjusting for age and sex. To take into account a potential family effect in GARP, shared frailty was applied in the Cox proportional hazard models (using STATA), assuming that observations of siblings have the same frailty. However, the variance of shared frailty was very small and including it had a negligible influence on the hazard ratios. We therefore performed the analyses without the family effect using SPSS version 20 (SPSS Inc, Chicago, IL, USA).

Results

Population descriptions

For the present analysis, 383 patients from the GARP cohort (mean age 60 years, 82% women; see online Supplementary Table S1) were included (one patient only seen at baseline and lost to follow-up), accounting for 3693 person-years of follow-up (median 9.9 years, range 1.83–11.9 years). In the OCC cohort, 459 patients (mean age 61 years, 88% women; Supplementary Table S1) were included (one patient only evaluated at baseline and lost to follow-up) and accounted for 1890 person-years of follow-up (median 3.9 years, range 0.87–6.8 years).

Mortality

In the GARP cohort, 26 OA patients (16 females, 10 males) died during follow-up, resulting in an SMR of 0.54 (95% CI 0.37–0.79). The SMR was lower in women than in men (Table 1). In patients from the OCC cohort we found similar results (Table 1). No excess mortality was observed in our two cohorts of OA patients when compared to the general population.

Causes of death

In the GARP study, 21 of the 26 deaths occurred due to either cancer (most common cause of death in women) or cardiovascular disease (most common cause of death in men) (Table 1).

Healthy cohort effect and sib pairs

A potential healthy cohort effect was investigated in the GARP cohort. The SMR did not increase when the start of follow-up was delayed (Figure 1). SMRs calculated separately for probands and siblings did not differ.

Table 1. Mortality and causes of death in two patient cohorts with primary osteoarthritis (OA), compared with the Dutch population.

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Cause of death</th>
<th>All patients</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Observed</td>
<td>Expected</td>
<td>SMR (95% CI)</td>
<td>Observed</td>
</tr>
<tr>
<td>GARP</td>
<td>All causes</td>
<td>26</td>
<td>48</td>
<td>0.54 (0.37–0.79)</td>
</tr>
<tr>
<td></td>
<td>Cardiovascular</td>
<td>9</td>
<td>14</td>
<td>0.66 (0.34–1.26)</td>
</tr>
<tr>
<td></td>
<td>Cancer</td>
<td>12</td>
<td>20</td>
<td>0.59 (0.33–1.04)</td>
</tr>
<tr>
<td>OCC</td>
<td>All causes</td>
<td>11</td>
<td>24</td>
<td>0.45 (0.25–0.82)</td>
</tr>
</tbody>
</table>

GARP, Genetics ARthrosis and Progression; OCC, Osteoarthritis Care Clinic; SMR, standardized mortality ratio; CI, confidence interval.
Risk factors associated with mortality

Univariate analysis revealed that male sex, increasing age, and self-reported cancer were associated with increased mortality in the GARP cohort. In multivariate analysis, male sex, age, and self-reported cancer were also associated with increased mortality. Hip OA was associated with mortality in the univariate analysis but not when adjustments were made for sex and age. The WOMAC questions on walking, walking on flat surfaces, and pain when walking were not associated with mortality. A strong trend can be seen for smoking (Table 2).

Discussion

In two observational cohorts of OA patients who consulted health-care services for their OA, no increased mortality rate was found. Risk factors for death were male sex, age, and the comorbid condition of cancer, but no OA-associated factors. These results suggest that management of OA patients may not need to focus specifically on treatment of cardiovascular risk factors and comorbidities.

Evidence concerning mortality in OA has been contradictory. Hochberg’s review concluded that an increased risk of death in OA with moderate evidence was due to methodological problems, such as lack of adjustment for confounding variables (7). Additionally, patients with hip and knee OA undergoing arthroplasty experienced prolonged survival. Our results are in line with these studies (8, 9).

Our findings do not support the results by Nuesch et al, who found excess mortality (1), possibly because of differences in study populations. The British cohort included subjects with knee or hip OA, recruited through a general population survey, whereas our cohorts included patients with knee or hip OA but also hand and spine OA who actively consulted health care from a medical specialist or general practitioner for their OA complaints.

We hypothesized that subjects who actively sought care for OA would be especially at risk for mortality because these patients would be suffering from severe forms of OA. However, our study results do not support this hypothesis. Several explanations can be proposed. These patients may be healthier because they possess behavioural traits that distinguish them from other OA patients who do not seek health care. These personality traits may also prompt them to pursue a healthy lifestyle and seek early care for diseases.

Both GARP and OCC participants were more often overweight when compared to the general population (5, 10). Although patients are not actively screened for

Table 2. Univariate and multivariate analyses of hazard ratios (HRs) with 95% confidence intervals (CIs) for mortality in 383 osteoarthritis (OA) patients.

<table>
<thead>
<tr>
<th>Characteristic at baseline</th>
<th>Univariate model HR (95% CI)</th>
<th>Multivariate model HR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>3.04 (1.38–6.69)</td>
<td>2.67 (1.21–5.90) **</td>
</tr>
<tr>
<td>Age (years)</td>
<td>1.10 (1.05–1.16)</td>
<td>1.10 (1.04–1.16) ***</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>0.98 (0.90–1.07)</td>
<td>0.97 (0.88–1.07)</td>
</tr>
<tr>
<td>Knee OA %</td>
<td>0.73 (0.31–1.73)</td>
<td>0.59 (0.25–1.41)</td>
</tr>
<tr>
<td>Hip OA §</td>
<td>2.31 (1.06–5.03)</td>
<td>1.55 (0.70–3.45)</td>
</tr>
<tr>
<td>AUSCAN pain ¶</td>
<td>0.95 (0.87–1.04)</td>
<td>0.98 (0.89–1.07)</td>
</tr>
<tr>
<td>AUSCAN function ¶</td>
<td>0.98 (0.93–1.03)</td>
<td>0.99 (0.94–1.04)</td>
</tr>
<tr>
<td>WOMAC pain ¶</td>
<td>0.99 (0.97–1.01)</td>
<td>0.99 (0.97–1.01)</td>
</tr>
<tr>
<td>WOMAC function ¶</td>
<td>0.99 (0.98–1.01)</td>
<td>1.00 (0.98–1.01)</td>
</tr>
<tr>
<td>Smoking</td>
<td>1.99 (0.87–4.58)</td>
<td>2.14 (0.91–5.04)</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>0.62 (0.08–4.54)</td>
<td>0.43 (0.06–3.18)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.77 (0.42–7.47)</td>
<td>1.14 (0.27–4.88)</td>
</tr>
<tr>
<td>Cancer</td>
<td>8.29 (3.12–22.03)</td>
<td>13.56 (4.69–39.19)</td>
</tr>
</tbody>
</table>

BMI, Body mass index; AUSCAN, Australian/Canadian Osteoarthritis Hand Index; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

* Adjusted for age and sex. ** Adjusted for age alone. *** Adjusted for sex alone.
† Patients without knee OA as the reference category
§ Patients without hip OA as the reference category
¶ HRs given per unit standardized score.
metabolic syndrome, patients with OA who consult health care will also receive care for other known medical conditions, which could result in lowered mortality rates. As we did not find any specific cause of death that stood out, or an effect of OA-related factors, these explanations seem more likely than an effect of OA per se on mortality.

Our study has some limitations. First, in a prosthetic study it has been suggested that reduced mortality may be explained by preoperative selection of healthier people (11). To exclude the possibility that our results may have resulted from exclusion of patients with a shortened lifespan in GARP, we tested for the presence of this ‘healthy cohort’ effect and did not find it. Exclusion of patients aged 75 years and older is unlikely to have biased our SMR, as the number of deaths in the age-matched general population would have been high as well. We also coped with this limitation by replication in the OCC cohort.

Second, the reliability of the death certificates, often filled in late at night, is limited. However, this misclassification will occur in our OA patients and control population alike. Self-reported diseases can also be misclassified.

Finally, cardiovascular disease, the WOMAC function, and body mass index (BMI) were not associated with mortality in our GARP cohort. These negative findings may be due to the limited number of events that occurred. Many unknown factors may act as confounders for the association between some factors and mortality (e.g. influence of NSAIDs on the association between physical function and mortality). Unfortunately, because of the limited number of events in our cohorts, we were unable to investigate the extensive list of potential confounders in this study.

Supporting Information

Additional Supporting Information may be found in the online version of this article.

Supplementary Table S1: Baseline characteristics of patients in the GARP study and ‘Osteoarthritis Care Clinic’ patients.

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Acknowledgements

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References