Concise report

Rheumatoid arthritis and the prevalence of diabetic retinopathy

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Abstract

Objective. RA increases vascular disease and angiogenesis, yet a 1964 Lancet report paradoxically linked RA to lower diabetic retinopathy. Our objective was to examine RA as a risk factor for diabetic retinopathy compared with other vascular risk factors.

Methods. This cohort study compared the prevalence of diabetic retinopathy in diabetes patients with and without RA in a 5% Medicare sample. We analysed the impact of RA on the prevalence of diabetic retinopathy using multivariate logistic regression calculating adjusted rate ratios (ARRs) controlling for sociodemographics, co-morbidity and health utilization. Sensitivity analysis examined eye exam rates.

Results. Among 256,331 Medicare diabetes patients, 5572 (2%) had RA. Diabetic retinopathy was less prevalent in patients with RA compared with those without RA (13.7% vs 16.1%, P < 0.01). Compared with patients without RA, the adjusted model demonstrated that patients with diabetes and RA were 28% less likely to have diabetic retinopathy and 4% more likely to receive an eye exam [ARR 0.72 (95% CI 0.67, 0.77), ARR 1.04 (95% CI 1.02, 1.06)].

Conclusion. Findings support the 1964 paradox observing decreased diabetic retinopathy in patients with RA. These findings pose new questions regarding whether RA physiology or treatments protect against diabetic retinopathy and how intraocular factors vary in contrast to adverse vascular changes elsewhere.

Key words: RA, diabetes, retinopathy, microvascular, epidemiology.

Rheumatology key messages

- Among Medicare patients with diabetes, RA patients had a lower prevalence of diabetic retinopathy.
- Potential ocular-protective RA treatments or intraocular factors despite vascular pathology elsewhere should be investigated.

Introduction

Although RA is an independent vascular disease risk factor, a 1964 Lancet article reported a lower incidence of diabetic retinopathy in diabetes patients with co-morbid RA [1]. At that time, the authors hypothesized that the reduction was linked to regular aspirin use. However, aspirin is no longer a RA mainstay, prompting interest in re-examining this relationship. Given that RA is known to adversely impact both microvascular and macrovascular physiology and increase cardiovascular events [2], as well as fuel angiogenesis [3], the 1964 report of lower diabetic retinopathy in RA seems paradoxical. Moreover, our earlier work showed less haemoglobin A1C testing in patients with both RA and diabetes mellitus compared with those without RA [4], predicting worse microvascular control.

The primary objective of this study was to examine the impact of RA on the prevalence of diabetic retinopathy. We hypothesized that patients with both RA and diabetes mellitus would have more diabetic retinopathy due to

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heightened microvascular dysfunction and macrovascular disease, increased angiogenesis and waning salicylate use in RA. Recognizing that up to 40% of Medicare-aged patients with diabetes and RA patients have received HCQ [5], creating dual indications for annual eye exams, a sensitivity analysis also compared exam rates.

Methods

Setting and participants
In this retrospective cohort study, beneficiaries aged 65 years and older continuously enrolled and alive from 2004 to 2006 were identified from a 5% random US Medicare sample as described in previous work [4]. Enrolment and claims data (2004–6) were extracted for all patients meeting the diabetes mellitus definition using a validated claims-based algorithm [6]. Patients were determined as having RA if they had two or more International Classification of Diseases, 9th edition (ICD-9) codes (714.0–714.33) on inpatient or outpatient claims at least 2 months apart in 24 months based on modified previously validated algorithms [7–8]. The Medicare denominator file was used to exclude beneficiaries without continuous Medicare Parts A and B coverage; those with incomplete data, including a health maintenance organization or railroad benefits; those who died and those with incomplete data, including a health maintenance organization or railroad benefits; those who died and those without outpatient encounters from 2004 to 2006, given the limited opportunity for disease monitoring. The Institutional Review Board at the University of Wisconsin approved the study and issued a waiver of informed consent.

Variables
Outcomes and baseline co-morbidities were established using validated Current Procedural Terminology and ICD-9 searches [9, 10]. Between 2004 and 2005, diabetic retinopathy was identified by ICD-9 codes indicating retinopathy (362.01, 362.02), macular oedema (362.8), retinal detachment (361.9) or vitreous haemorrhage (379.23 or 14.7 procedure) [10]. Receipt of eye exams in 2006 was assessed by searching carrier, outpatient or inpatient facility claims for eye exams per validated protocols [9].

Baseline sociodemographics, co-morbidities and health care utilization were assessed using Medicare claims data and the Medicare denominator file as previously described [4]. In addition, risk adjustment was evaluated using the Centers for Medicare and Medicaid Services Hierarchical Condition Categories score, as previously described [4].

Analysis
Descriptive statistics included analysis of variance to compare continuous baseline characteristics and chi-squared analysis to compare categorical data. Multivariable logistic regression with robust estimates of the variance was used to analyse the relationship between explanatory variables and the presence of diabetic eye disease or eye screening. Predicted probabilities, adjusted risk ratios (ARRs) and odds ratios (ORs) for testing were calculated for diabetes patients with and without co-morbid RA. Age, gender, race/ethnicity, Medicaid buy-in, Rural–Urban Commuting Area (RUCa) category, Hierarchical Condition Categories quartile, hospitalization during 2004–2006 and other specific co-morbidities, including major diabetic complications [peripheral vascular disease (PVD), lower extremity ulcers, amputation and chronic kidney disease (CKD)], cardiovascular disease (CVD), hyperlipidaemia, orthopaedic surgery, gait-assistance device, total number of unique providers seen by quartile and visit frequencies, were also included within logistic models based on theoretical importance.

Analyses were conducted using SAS version 9.1.3 (SAS Institute, Cary, NC, USA) and Stata version 10.0 (StataCorp, College Station, TX, USA). Adjusted predicted probabilities were estimated based on the recycled predictions approach using the Stata margins command, which facilitated ARR calculation [11]. ARR comparison was included, given the methodological benefits of this approach when interpreting common outcomes [12]. The recycled predictions approach predicts the outcome assuming that everyone in the dataset is treated as if they first did and then did not have the characteristic in question (e.g. RA vs no RA), keeping other covariates set at their naturally occurring values. CIs were calculated using the delta method and allowed correlation between observations (analogous to the robust option) to estimate the logistic regression [11].

Results
Table 1 displays the baseline characteristics of our final sample of 256 331 Medicare beneficiaries with diabetes mellitus, further categorized as 5572 with RA and 250 759 without RA. Diabetes patients with RA were more likely to be female and have received Medicaid compared with diabetes patients without RA. As depicted in Table 1, PVD and CKD were more common in patients with co-morbid diabetes mellitus and RA compared with patients with only diabetes mellitus (43.3% vs 32.9%, P ≤ 0.01; 17.1% vs 14.4%, P ≤ 0.01, respectively).

Before adjustment, patients with both RA and diabetes mellitus had lower prevalence of diabetic retinopathy (13.7% vs 16.1%, P ≤ 0.01). The adjusted model demonstrated that diabetes mellitus patients with co-morbid RA were 28% less likely to have diabetic retinopathy than patients without RA [ARR 0.72 (95% CI 0.67, 0.77)]. Furthermore, when compared with other vascular co-morbidities, RA was the only condition linked with a lower prevalence of diabetic retinopathy, while other conditions such as ischaemic heart disease, PVD and CKD each independently increased the risk for diabetic retinopathy (Fig. 1). When comparing a separate model restricted to RA patients without a history of other diabetes complications, the significantly lower prevalence of diabetic retinopathy persisted compared with diabetes patients without RA [OR 0.71 (95% CI 0.58, 0.87), data not shown].

Overall, 66% of patients with co-morbid RA compared with 62.5% of patients with diabetes mellitus and no RA
received eye exams. The adjusted model showed that co-morbid diabetes mellitus and RA patients were 4% more likely to get exams [ARR 1.04 (95% CI 1.02, 1.06), data not shown].

Discussion

In this national cohort study, we observed decreased prevalence of diabetic retinopathy in diabetes patients with co-morbid RA compared with diabetes patients without RA. Our earlier work reported less haemoglobin A1C testing in those with diabetes mellitus and RA, which would have predicted more diabetic retinopathy [4]. In contrast, findings here show that diabetic retinopathy was less prevalent in patients with RA, consistent with the 1964 Lancet report [1].

Our findings, along with those from the original Lancet report, suggest that RA and/or RA treatments might be protective for diabetic retinopathy. Growing evidence links a number of inflammatory and immunological mechanisms in the pathogenesis of diabetic retinopathy that may be relevant when considering the relationship. In particular, studies suggest that cyclooxygenase (COX) enzymes, pro-inflammatory prostaglandins and thromboxanes are key players in retinopathy progression [13, 14]. Furthermore, as summarized in a recent review, diabetic retinopathy involves increased blood flow, inflammatory cytokine expression and accelerated cell death [13]. RA activity may increase angiogenesis and endothelial precursor dysfunction, while treatments such as anti-TNF agents, other biologics or even glucocorticoids can halt angiogenic and endothelial dysfunction [3]. Theoretical explanations for decreased diabetic retinopathy in the RA population may therefore include therapies such as NSAIDs, salicylates, anti-TNFs and CSs or RA physiology. We were unable to directly test this due to the absence of prescription medication data for Medicare beneficiaries prior to 2006. Alternatively, distant angiogenesis or circulating anti-angiogenic and anti-inflammatory factors in treated RA may keep retinopathy in check. In various solid tumours, primary tumours can suppress metastatic angiogenesis until primary tumour removal leads to massive metastatic growth [15]. Analogously, locally angiogenic RA activity or circulating anti-angiogenic or endothelial factors may exert retinal protection.

Recently, numerous studies have attempted to treat diabetic retinopathy with topical and systemic NSAIDs, salicylates, CSs and anti-TNF-α agents. A murine study demonstrated a significant reduction in retinal endothelial cell death and injury in rats treated with the anti-TNF etanercept compared with non-treated controls [16]. Another murine study tested aspirin, sodium salicylate and SSZ, showing slowed degeneration of retinal capillaries and ganglion cell loss [17]. In addition, both systemic and topical NSAID trials have shown slowed progression of diabetic retinopathy by targeting the COX enzyme pathways [18]. These agents may explain the observed protection in diabetes patients with RA.

Strengths of our study include the power of this large, nationally representative sample of Medicare patients with diabetes and RA and the use of validated algorithms. However, our results should be interpreted in the light of a few limitations. First, given the limits of most national administrative claims studies, we could not perform

### Table 1: Characteristics of Medicare diabetes patients with and without RA (n = 256331)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (n = 256331)</th>
<th>Diabetes + RA (n = 5572)</th>
<th>Diabetes no RA (n = 250759)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sociodemographics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, mean (s.d.), years</td>
<td>74.3 (6.3)</td>
<td>74.3 (6.2)</td>
<td>74.3 (6.4)</td>
<td>—</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>156010 (60.9)</td>
<td>4164 (74.7)</td>
<td>151846 (60.6)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>White race/ethnicity, n (%)</td>
<td>211883 (82.7)</td>
<td>4318 (77.5)</td>
<td>207565 (82.8)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Medicaid (ever), n (%)</td>
<td>48424 (18.9)</td>
<td>1480 (26.6)</td>
<td>46944 (18.7)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><strong>Baseline diabetes complication profile, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>84850 (33.1)</td>
<td>2410 (43.3)</td>
<td>82440 (32.9)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>36936 (14.4)</td>
<td>952 (17.1)</td>
<td>35984 (14.4)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Lower extremity ulcers</td>
<td>18518 (7.2)</td>
<td>703 (12.6)</td>
<td>17815 (7.1)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Amputation</td>
<td>1637 (0.64)</td>
<td>50 (0.9)</td>
<td>1587 (0.6)</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

**Fig. 1 Adjusted risk ratios for diabetic retinopathy**

The vertical line indicates the reference group at ARR = 1.0. CHF: congestive heart failure; CKD: chronic kidney disease; DM: diabetes mellitus; IHD: ischaemic heart disease; MI: myocardial infarction; PVD: peripheral vascular disease; TIA: transient ischaemic attack.
individual case validation in this Medicare claims study. Second, we were unable to directly test the hypotheses that RA agents were individually protective, given the absence of pharmacy data in Medicare claims prior to 2006. Although salicylate treatment for RA has declined in recent decades, it is possible that aspirin (ASA) use may still be higher among diabetes patients with RA compared with those without RA. In the National Health and Nutrition Examination Survey III, only 37% of diabetes patients with known CVD reported regularly using ASA, and an RA patient survey reported regular ASA use in only 18% of patients, although the combined prevalence has not been reported [19]. Moreover, given data limitations, we were unable to control for smoking and the duration or control of diabetes, which are all major determinants for diabetic retinopathy. Codes for diabetes with retinopathy (250.50–250.53) were omitted without separate validated retinopathy codes, however, this should not be different with or without RA, thus not biasing point estimates. We also did not control for diabetic neuropathy, given the absence of a validated algorithm at the time of our study. In addition, patients who died prior to the end of follow-up were excluded; however, if more diabetes patients with RA compared with diabetes patients without RA died, e.g. due to ischaemic heart disease, then survivors with diabetes and RA could be healthier than other patients with diabetes, leading to lower observed retinopathy. Lastly, our findings may not be generalizable to younger or non-Medicare patients, and billing codes and claims may not be error free; however, our group utilized validated algorithms to identify patients and outcomes. This large, nationally represented sample generates interesting hypotheses regarding possible protective effects of RA and/or RA treatments in diabetic retinopathy that should be investigated in future studies.

The evidence presented in this study shows a lower prevalence of diabetic retinopathy despite more eye exams in patients with co-morbid diabetes and RA. Findings highlight the need for studies examining the potential protective benefits of therapies such as NSAIDs, salicylate, CS and anti-TNF-α in the retina, or other potential pathways mediating ocular protection in RA patients with diabetes mellitus. These findings pose new questions regarding whether RA physiology or treatments protect against diabetic retinopathy and how intracellular factors vary in contrast to adverse vascular pathology elsewhere.

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