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Achilles or biceps tendon rupture in women and men with type 2 diabetes: A population-based case–control study

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ABSTRACT

Aims: Previous studies suggest that diabetes causes alterations in tendon collagen structure, but evidence on how such findings translate into clinical practice is scarce. We aimed to analyze the association between type 2 diabetes and the risk of tendon rupture.
Materials and methods: We conducted a matched case–control analysis using the UK-based Clinical Practice Research Datalink. Cases (n = 7895) were aged 30–89 years and had an incident diagnosis of Achilles- or biceps tendon rupture between 1995 and 2013. In multivariable logistic regression analyses we compared the odds of tendon rupture between patients with or without type 2 diabetes, in men and women separately, and taking into account diabetes severity (HbA1c), duration, and antidiabetic drug treatment.
Results: Within 165 (7.1%) female cases with type 2 diabetes, odds ratios (ORs) were increased with poorer diabetes control (OR 2.03, 95% CI 1.20–3.41, HbA1c ≥9% [≥75 mmol/mol]), longer disease duration (OR 1.60, 95% CI 0.93–2.74, ≥10 years), and current insulin use (OR 2.25, 95% CI 1.30–3.90, ≥20 prescriptions). Among 372 (6.7%) male cases, there was no effect of type 2 diabetes on the risk of tendon rupture.
Conclusions: Our results suggest that the risk of tendon ruptures may be increased in women with poorly controlled type 2 diabetes, but not in men.

1. Introduction

Achilles- and biceps tendon ruptures are the most frequent types of tendon ruptures, of which Achilles tendon ruptures (ATRs) predominantly occur in middle aged men during sport activities, whereas biceps tendon ruptures (BTRs) often occur spontaneously as a result of chronic tendinopathy and other shoulder pathologies in elderly patients (Elser, Braun, Dewing, Giphart, & Millett, 2011; Lantto, Heikkinen, Flinkkilä, Ohtonen, & Leppilahti, 2014; Raikin, Garras, & Krapchev, 2013; Snyder, Mair, & Lattermann, 2012). Pre-existing tendon damage increases the risk of rupture at little or no extrinsic stress (Cook, Khan, & Purdam, 2002; Longo et al., 2011; Seeger et al., 2006; Vosseller et al., 2013), but evidence on factors that compromise tendon integrity is scarce; overuse, advanced age, male sex, obesity, genetic factors, and various systemic diseases (e.g. adrenal disorders, chronic kidney disease, or different rheumatic diseases) have been considered (Magnan, Bondi, Pierantoni, & Samaila, 2014).

Preclinical studies have reported tendon alterations and inferior biomechanical properties of animal tendons in association with diabetes (Boivin et al., 2014; Zakaria, Davis, & Davis, 2014). Small observational imaging studies, further reported increased tendon thickening and collagen disorganization of tendons in patients with type 2 diabetes (Abate, Salini, Antinolfi, & Schiavone, 2014; Connizzo, Bhatt, Liechty, & Soslowsky, 2014; de Jonge et al., 2015; de Oliveira, Lemos, de Castro Silveira, da Silva, & de Moraes, 2011). Overall, this small body of evidence suggests that type 2 diabetes may be associated with some degree of tendon alteration, but methodologic heterogeneity, insufficient consideration of potential effect modifiers (e.g. age, sex, type 2 diabetes duration), and limited sample size preclude comparison of results and identification of patients at greatest risk (Abate et al., 2014; Connizzo et al., 2014; de Jonge et al., 2015; de Oliveira et al., 2011). Presence of diabetic neuropathy (Giacomozzi, D'Ambrogi, Uccioli, & Macellari, 2005), female sex, and poorly controlled glucose levels have been reported to correlate with the degree of tendon alterations (Akturk, Ozdemir, Maral, Yetkin, & Arslan, 2007; Papanas et al., 2009). One observational cohort study quantified the risk of hospitalization due to any tendon rupture and

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reported a 44% increased risk (mostly rotator cuff injury) in type 2 diabetes patients of either sex compared to patients without diabetes (Zakaria et al., 2014). Except for one case report linking bilateral Achilles tendinitis to therapy with sitagliptine, which resolved after therapy cessation (positive dechallenge), we are not aware of any previous studies, which assessed antidiabetic drugs in association with tendinopathies (Bussey, Emanuele, Lomasney, & Tehrani, 2014).

We aimed to evaluate the risk of ATR/BTR in patients with or without type 2 diabetes in men and women separately, by type 2 diabetes severity, duration, and drug treatment, and by the presence of recorded diabetes-specific complications (i.e. neuropathy, retinopathy, and chronic kidney disease) in a large observational study using data from the primary care setting in the UK.

2. Subjects and methods

2.1. Study design and data source

We conducted a case–control analysis using data from the UK-based Clinical Practice Research Datalink (CPRD). The CPRD is a large anonymous primary-care database comprised of approximately 10 million patients enrolled with selected general practitioners (GPs). In the UK, GPs hold a gatekeeper role within the National Health System (NHS). After referrals, consultants are required to send information on outpatient diagnoses and treatments to the GP who enters this information into the database and takes over long-term care. Participating practices provide information on patient demographics and characteristics (e.g. age, sex, height, weight, smoking status), symptoms or diagnoses, lab test results, and referrals to secondary care. Drug prescriptions are generated electronically via computer, ensuring a virtually complete outpatient drug history. The Medicines and Healthcare Products Regulatory Agency (MHRA) checks the raw data before release and performs quality control checks. The patients enrolled in the CPRD are representative of the UK population with regard to age, sex, and annual turnover rate. Extensive validation of the CPRD has documented its high validity, especially for chronic conditions (Herrett et al., 2015). The database has been the source of numerous pharmacoepidemiological and disease epidemiology studies (Herrett et al., 2015). The study protocol was approved by the Independent Scientific Advisory Committee for MHRA database research.

2.2. Cases

We identified all patients in the CPRD aged 30 to 89 years with an incident Read code for ATR or BTR between January 1995 and December 2013. Patients were not eligible if they had a record for a previous rupture of or manipulation on the Achilles or biceps tendon, or in case of a recorded acquired or congenital malformation of the respective tendon. Furthermore, all patients were required to have ≥3 years of recorded active history in the database prior to the date of the ATR/BTR diagnosis ('index date') to increase the likelihood of only including incident cases. We excluded patients with a Read code for alcoholism, substance abuse, cancer (except non-melanoma skin cancer), or HIV prior to the index date, as these patients are subject to bias and confounding. We also excluded patients with a record for a major accident (e.g. vehicle accident, fall from roof or ladder) within 30 days prior to the index date, to exclude patients with tendon ruptures caused by exceptional extrinsic stress. Cases with indirect trauma, such as sporting accidents, were not excluded. We did not exclude patients with previous Achilles or biceps tendinitis as this may precede tendon rupture and may thus lie on the causal pathway (Kirchgesner et al., 2014; Snyder et al., 2012).

2.3. Controls

We randomly matched 4 controls to each case on age (year of birth), sex, general practice, calendar time (index date), and number of years of recorded history in the database prior to the index date, and we applied the same exclusion criteria to controls as to cases.

2.4. Exposure

Previous studies validated diabetes diagnoses recorded in the CPRD and reported a positive predictive value of 98.6% (95% CI 92.2–100.0) (Khan, Harrison, & Rose, 2010). We defined diabetes exposure as one or more recorded Read-code for type 2 diabetes (ICD-10 E11 and E14) prior to the index date, and classified type 2 diabetes patients as incident (i.e. ≥365 days of active history prior to the first recorded diabetes diagnosis or antidiabetic drug prescription) or prevalent diabetics (all non-incident type 2 diabetes patients). Among incident diabetes patients, we captured diabetes disease duration, defined as the number of years between the first recorded diabetes diagnosis and the index date. We further assessed the average recorded HbA1c value prior to the index date wherever available, and whether the patient had a previous record for diabetic neuropathy, retinopathy, or chronic kidney disease. We defined mutually exclusive categories of antidiabetic drug treatment: untreated type 2 diabetes, metformin use only (stratified by timing [last prescription <180 days] and duration of use [number of prescriptions]), sulfonylurea use (+/− metformin, stratified by timing and duration of use), other treatment, or combined oral therapy, or insulin use (+/− oral antidiabetics, stratified by timing and duration of use).

2.5. Statistical analysis

We conducted multivariable conditional logistic regression analyses to evaluate the association between type 2 diabetes and the risk of incident ATR/BTR using SAS statistical software (version 9.4, NC, US). Relative risk estimates were calculated as odds ratios (ORs) with 95% confidence intervals (CIs), separately for men and women. We evaluated type 2 diabetes exposure by duration (in incident type 2 diabetes patients only) and disease severity (average HbA1c level), by the presence of diabetes-specific complications (i.e. neuropathy, retinopathy, and chronic kidney disease) as well as by antidiabetic drug treatment. We also stratified analyses by age (</≥65 years) and index diagnosis (ATR or BTR). Based on clinical knowledge, we *a priori* defined potential confounders which were included in the multivariable model. These were smoking (non, current, ex, unknown), alcohol consumption (none, </≥14 units/week, or unknown), body mass index (BMI, <18.5, 18.5–24.9, 25.0–29.9, 30+ kg/m^2, or unknown), and the following comorbidities recorded prior to the index date; osteoporosis, osteoarthritis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vasculitis, polymyalgia rheumatica, gout, hypertension, hyperlipidemia, myocardial infarction, ischemic heart disease, and congestive heart failure. We further adjusted for concomitant use (last prescriptions <180 days prior to the index date) of fluoroquinolone antibiotics, hormone replacement therapy, fibrates, and oral corticosteroids.

While ATR is a relatively straightforward diagnosis (Cook et al., 2002), BTR is more complicated to diagnose and frequently coexists with other shoulder pathologies. However, imaging procedures, such as ultrasound, MRI, arthrograms, or X-ray are established tools to diagnose ATR as well as BTR (Ejnisman, Monteiro, Andreoli, & de Castro Pochini, 2010; Snyder et al., 2012; Thevendran, Sarraf, Patel, Sadri, & Rosenfeld, 2013). In a sensitivity analysis we therefore identified those ATR/BTR patients whose diagnosis was preceded (within 180 days) by a recorded diagnostic imaging procedure or by a consultation to a specialist, and repeated the analysis stratified by disease severity and duration in this subsample.