Cirrhosis is a risk factor for total hip arthroplasty for avascular necrosis

A Danish nationwide cohort study

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Background and purpose — There are limited data on risk factors for avascular necrosis of the hip, but cirrhosis has been proposed as a risk factor. We examined the association between cirrhosis and incidence of total hip arthroplasty for avascular necrosis.

Methods — We used nationwide healthcare data to identify all Danish residents diagnosed with cirrhosis in 1994–2011, and matched them 1:5 by age and sex to non-cirrhotic reference individuals from the general population. We excluded people with a previous total hip arthroplasty, a previous hip fracture, or a previous diagnosis of avascular necrosis. We used stratified Cox regression to estimate the hazard ratio (HR) for cirrhosis patients relative to reference individuals, adjusting for potential confounders. We used the cumulative incidence function to compute 5-year risks.

Results — We included 25,421 cirrhosis patients and 114,052 reference individuals. Their median age was 57 years, and 65% were men. 45 cirrhosis patients and 44 reference individuals underwent total hip arthroplasty for avascular necrosis. Cirrhosis patients' HR for a total hip arthroplasty for avascular necrosis was 10 (95% CI: 6–17), yet their 5-year risk of avascular necrosis was only 0.2%. For the reference individuals, the 5-year risk was 0.02%.

Interpretation — Cirrhosis is a strong risk factor for avascular necrosis of the hip, but it is rare even in cirrhosis patients.

Cirrhosis is the end-stage of all chronic liver diseases. It leads to a profound disturbance of the systemic circulation (Vallance and Moncada 1991), of the immune response (Lin et al. 2007), and of the coagulation system (Northup and Caldwell 2013), but whether cirrhosis is a risk factor for joint disease has not been determined. Avascular necrosis (AVN) is bone necrosis caused by insufficient circulation, predominantly affecting bone parts with poor circulation: the femoral head and to a lesser extent the femoral condyles and carpal bones (Chang et al. 1993). The pathogenesis of AVN remains poorly understood, but risk factors include tobacco smoking (Hirota et al. 1993, Matsuo et al. 1988), corticosteroid treatment (Guo et al. 2014), alcoholism (Hirota et al. 1993, Matsuo et al. 1988), fractures (Loizou and Parker 2009), and certain other conditions (Mankin 1992). Hung et al. (2011) reported that cirrhosis may also be a risk factor. Their study compared the risk of AVN in cirrhosis patients and that in an age-matched cohort of hospitalized patients with a high prevalence of conditions that predispose to AVN. They may therefore have underestimated the strength of the association. AVN is clinically significant because many AVN patients require total hip arthroplasty (THA), and both AVN and cirrhosis are associated with an increased risk of complications after total hip arthroplasty (Bergh et al. 2014, Jiang et al. 2014, Deleuran et al. 2015).

We investigated the association between cirrhosis and AVN of the hip. This might help us understand the pathogenesis of avascular necrosis, and that is the first step towards preventing or treating the condition without surgery.

Methods

Data sources

We performed this registry-based historical cohort study in Denmark, which has 5.6 million inhabitants. All Danish residents are given universal, tax-paid access to hospitals. The Danish National Patient Registry (NPR) is a nationwide registry that has covered admissions to non-psychiatric hospitals since 1977 and outpatient and emergency room visits since 1995. The data include relevant dates and discharge diagnoses, coded in accordance with the International Classification

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of Diseases, 10th edition (ICD-10) from 1994 and the ICD-8 before that (Lynge et al. 2011). The Danish Hip Arthroplasty Registry (DHR) is a clinical database of all primary or revision total hip arthroplasties performed in Denmark since January 1, 1995. The data are entered by the operating surgeon immediately after the procedure and include the indication for arthroplasty (primary osteoarthritis, fracture, avascular necrosis, or other indication) (Pedersen et al. 2004). The indication for arthroplasty has been confirmed by medical chart review and radiographs in 79 of 80 randomly selected AVN patients (Pedersen et al. 2004). The Danish Central Office of Civil Registration continuously monitors the vital status of Danish residents, including dates of emigration or death, and it issues a unique personal identification number to everyone at birth or immigration. This number enables linkage of individual-level data between the NPR, the DHR, and the civil registration system (Pedersen et al. 2006).

Cirrhosis patients and reference individuals

We identified all Danish residents with a first-time hospital discharge diagnosis of alcoholic cirrhosis (ICD-10: K70.3, K70.4) or unspecified cirrhosis (ICD-10: K74.6) between 1994 and 2011. Biopsy or clinical evaluation had confirmed 85% of diagnoses for cirrhosis in the NPR in a previous validation study (Vestberg et al. 1997). We defined the "index date" as the date of the first cirrhosis diagnosis. To study the association between cirrhosis and a total hip arthroplasty for AVN, we excluded cirrhosis patients if they had a previous diagnosis of avascular necrosis (ICD-10: M87.0), if they had previously undergone total hip arthroplasty, or if they were diagnosed with hip fracture (ICD-8: 820.xx, 821.xx, 822.xx, 823-xx; ICD-10: S72.0, S82.0, S82.1, S83.x) before the index date. We matched these cirrhosis patients 1:5 on the basis of age, sex, and birth date to reference individuals without cirrhosis from the general Danish population, using risk-set sampling (Langholz and Goldstein 1996). The reference individuals were given the same index date as the corresponding cirrhosis patient. We excluded reference individuals according to the same criteria as cirrhosis patients; this exclusion resulted in a situation whereby not all cirrhosis patients were matched 1:5.

Confounders

The NPR holds data on potential confounders of an association between cirrhosis and AVN. We identified previous emergency room visits, inpatient and outpatient hospitalizations for conditions predisposing to AVN (diabetes, HIV infection, myeloproliferative disease, hemoglobinopathy, chronic renal failure, gout, and solid organ transplantation), an indicator of smoking (chronic obstructive pulmonary disease), and indicators of corticosteroid treatment (autoimmune hepatitis, rheumatoid arthritis, and connective tissue disease) (diagnosis codes are shown in Table 1). As an indicator of alcohol intake, we identified emergency room visits and inpatient and outpatient hospitalizations for alcoholism or alcohol-related disorders before the index date (see Supplementary data, Table 3).

Outcomes and statistical analysis

We examined one outcome: time to total hip arthroplasty for AVN. We followed the cirrhosis patients and the reference individuals from the index date to the date of total hip arthroplasty for AVN, date of death, or end of follow-up (December 31, 2011). We used stratified Cox regression to estimate the hazard ratio (HR) of total hip arthroplasty for AVN in cirrhosis patients as opposed to reference individuals and adjusted these HRs for potential confounders. We found no violations of the proportional hazards assumption when we tested it using Schoenfeld residuals and checked it by inspecting the log-log plot. We used the cumulative incidence function with death as a competing risk to compute the 5-year risk of total hip arthroplasty for AVN. This analysis relies on non-informative censoring. There were 2 censoring events in our study cohort: end of study (on December 31, 2011) and migration. Both of these events are unlikely predictors of the risk of a total hip arthroplasty for AVN, so the censoring in our study cohort was non-informative. Alcohol intake is a well-known risk factor for AVN, and cirrhosis patients have a high prevalence of alcohol intake. We were concerned that the regression analysis would leave residual confounding, so we performed a supplementary analysis in which we used restriction to minimize confounding by alcohol intake. We repeated the regression analysis and restricted it to cirrhosis patients with unspecified cirrhosis (ICD-10: K74.6) who had not been hospitalized for an alcohol-related disorder (see Supplementary data, Table 3), and the corresponding reference individuals. Reference individuals who had previously been hospitalized for an alcohol-related disorder were also left out of this analysis. All statistical analyses were performed using Stata version 12.1 and the R software package version 2.14 (R 2013).

Results

We included 25,421 cirrhosis patients and 114,052 reference individuals. Their median age was 57 years and 65% were male. 45 cirrhosis patients and 44 reference individuals underwent total hip arthroplasty for AVN. Diabetes and COPD were the most prevalent confounders, and the majority of confounders were more prevalent in cirrhosis patients than in reference individuals (Table 1). Cirrhosis patients' adjusted HR for a total hip arthroplasty for AVN was 10 (95% CI: 6–17). Both cirrhosis patients' and reference individuals' 5-year risk of a total hip arthroplasty for AVN was very low, but it was markedly higher in cirrhosis patients: 0.16% (95% CI: 0.12–0.23) vs. 0.02% (95% CI: 0.01–0.03). Cirrhosis patients' HR for a total hip arthroplasty for AVN was essentially unaltered in our supplementary analysis, restricted to patients without alcoholic cirrhosis (Table 2).

Table 1. Prevalence of risk factors for AVN at the index date, with ICD-8 and ICD-10 codes

	ICD-8	ICD-10	Cirrhosis patients (%)	Reference individuals (%)
Conditions predisposing to AVN				
Diabetes mellitus	249.xx, 250.xx	E10.x–E14.x	13	4
HIV	079.83	B20.x–B24.x	0.26	0.06
Myeloproliferative disease	20x.xx	C88.x, C90–96.x	0.71	0.33
Hemoglobinopathy	282.xx	D55.x– D59.x	0.36	0.05
Chronic renal failure	58x.xx	N18.x	1.2	0.37
Gout	274.0x	M10.x	2.1	0.49
Solid organ transplantation	Y95.xx	Z94.x	0.28	0.15
Indicator of smoking				
Chronic obstructive lung disease	490.xx–492.xx	J43.x–J44.x	7.2	2.4
Indicator of corticosteroid treatment				
Autoimmune hepatitis	573.02	K73.2, K75.4	0.90	0.02
Rheumatoid arthritis	712.0x–712.2x	M05.x	0.56	0.44
Connective tissue disease	734.xx	M3x.x	0.73	1.2

Table 2. Results of the main regression analysis and the supplementary regression analysis

	No. of cirrhosis patients (with AVN)	No. of reference individuals (with AVN)	Unadjusted HR [a] (95% CI)	Adjusted HR [b] (95% CI)
Main analysis	23,421 (45)	114,052 (44)	9.9 (5.8–17)	10 (5.8–17)
Supplementary analysis	4,977 (9)	21,851 (11)	13 (3.5–48)	12 (3.3–47)

[a] Unadjusted hazard ratio of THA for AVN in cirrhosis patients vs. reference individuals
[b] Adjusted hazard ratio of THA for AVN in cirrhosis patients vs. reference individuals, adjusted for other risk factors for AVN; see Table 1.

Discussion

We performed a nationwide cohort study and found a strong association between cirrhosis and total hip arthroplasty for avascular necrosis. This association was unaltered when we performed a supplementary analysis to minimize the influence of alcohol intake on our results. The absolute risks of a total hip arthroplasty for AVN were low, but markedly higher in cirrhosis patients than in reference individuals.

The main strength of this study was its population-based design and complete follow-up. One possible limitation was the validity of our data sources. NPR diagnoses for cirrhosis have previously been validated with biopsy or clinical evaluation as the gold standard. Cirrhosis was confirmed in 85% of patients with this diagnosis in the NPR (Vestberg et al. 1997), and the bias introduced by misclassifying individuals without cirrhosis as cirrhosis patients, or vice versa, would cause us to underestimate the true strength of the association between cirrhosis and AVN. The indication for hip arthroplasty in the DHR has been validated, showing that the positive predictive value for AVN was 99% (Pedersen et al. 2004). Still, it is possible that orthopedic surgeons are reluctant to perform arthroplasties in patients with cirrhosis, who have a high risk of postoperative complications (Deleuran et al. 2014). However, such a bias would cause us to underestimate the risk of total hip arthroplasty for AVN and also the strength of the association between cirrhosis and total hip arthroplasty for AVN. Thus, bias is unlikely to explain the strong association between cirrhosis and AVN.

Incomplete confounder control could possibly have led us to overestimate the effect of cirrhosis on the rate of total arthroplasty for AVN. We were able to adjust for conditions that predispose to AVN and for indicators of smoking and treatment with corticosteroids, but our use of hospital diagnoses to identify confounders would probably underestimate their prevalence. Our results were unaltered when we performed a supplementary analysis aimed at minimizing the effect of alcohol intake. Still, we cannot rule out the possibility that some of the association was caused by alcohol intake and other confounders, but we believe that it is unlikely that the strong association was entirely the result of confounding.

Hung et al. (2011) found an HR for AVN of 2.5 in a cohort of patients with cirrhosis (primarily due to viral hepatitis) relative to an age-matched cohort of hospitalized patients without cirrhosis. These hospitalized patients without cirrhosis had a high prevalence of conditions that predispose to AVN, but the reported associations were only adjusted for conditions recorded at the index hospitalization. Such incomplete recording of confounders may have resulted in residual confounding, which would have caused Hung et al. to underestimate the true strength of the association.

The mechanisms behind the association between cirrhosis and AVN are unclear. Cirrhosis patients suffer from coagulopathy, endothelial dysfunction, and chronic inflammation (Albillos et al. 2014, Iwakiri and Groszmann 2007, Søgaard et al. 2009). Endothelial dysfunction has been linked to glucocorticoid-induced AVN (Chen et al. 2013), but chronic inflammation may be more important for development of AVN (Morse et al. 2013). Interleukin-33, a T-lymphocyte activator, has been linked to both cirrhosis and AVN (Marvie et al. 2010, Zheng et al. 2014), and cirrhosis patients' hyperdynamic circulation facilitates diffusion of proinflammatory cytokines and endotoxins throughout the body (Lee et al. 1996). Hence, even though the exact mechanisms remain unclear, the pathophysi-

ology of cirrhosis shows a number of characteristics that have been associated with AVN, so a causal link between cirrhosis and AVN is plausible.

In conclusion, cirrhosis is a strong risk factor for avascular necrosis requiring total hip arthroplasty, but avascular necrosis is a rare condition, even in cirrhosis patients.

Supplementary data

Table 3 is available on the Acta Orthopaedica website (www.actaorthop.org), identification number 7581.

No competing interests declared.

TD and PJ analyzed and interpreted the data. TD, SO, HV, and PJ conceived and designed the study, and wrote the manuscript.

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