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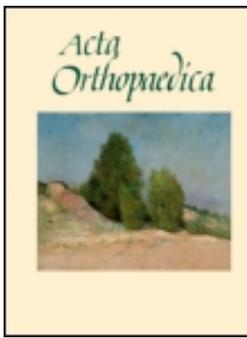
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Cirrhosis patients have increased risk of complications after hip or knee arthroplasty

A Danish population-based cohort study

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Background and purpose — The risk of complications in cirrhosis patients after orthopedic surgery is unclear. We examined this risk after total hip arthroplasty (THA) or total knee arthroplasty (TKA).

Patients and methods — Using Danish healthcare registries, we identified all Danish residents who underwent a THA or TKA for primary osteoarthritis in the period 1995–2011. We compared the risk of complications in patients with or without cirrhosis.

Results — The surgical technique was similar in the 363 cirrhosis patients and in 109,159 reference patients, but cirrhosis patients were more likely to have been under general anesthesia (34% vs. 23%), were younger (median age 66 vs. 69 years), had a predominance of males (54% vs. 41%), had more comorbidity, and had had more hospitalizations preoperatively. Their risk of intraoperative complications was similar to that for reference patients (2.5% vs. 2.0%), but they had greater risk of dying during hospitalization or within 30 days of discharge (1.4% vs. 0.4%; aOR = 3.9, 95% CI: 1.5–10); greater risk of postoperative transfer to an intensive care unit (0.6% vs. 0.06%; aOR = 5.8, CI: 1.3–25) or a medical department (4.4% vs. 2.5%; aOR = 1.7, CI: 0.99–2.9); greater risk of readmission within 30 days of discharge (15% vs. 8%; aOR = 1.8, CI: 1.3–2.4); and greater risk of deep prosthetic infection (3.1% vs. 1.4%) or revision (3.7% vs. 1.7%) within 1 year. The chance of having an uncomplicated procedure was 81.0% (CI: 76.6–85.0) for cirrhosis patients and 90.0% (CI: 89.6–90.0) for reference patients.

Interpretation — Cirrhosis patients had a higher risk of postoperative complications after THA or TKA for primary osteoarthritis than patients without cirrhosis. This may have implications for orthopedic surgeons' postoperative management of cirrhosis patients, and preoperative assessment by a hepatologist may be indicated.

Liver cirrhosis is the common end stage of all chronic liver diseases, and it affects about 0.2% of the Danish population. Alcohol is by far the most common cause of cirrhosis in Denmark. The number of total hip arthroplasties (THAs) and total knee arthroplasties (TKAs) performed is on the increase. Thus, it is also likely that more cirrhosis patients will undergo THA or TKA, particularly with the growing number of patients with cirrhosis related to obesity and non-alcoholic fatty liver disease. In cirrhosis patients, their portal hypertension, hyperdynamic circulation, and acquired immune deficiency is associated with an increased risk of complications after abdominal surgery (Ziser et al. 1999, Thulstrup et al. 2001, Nielsen et al. 2002, Friedman 2010), but it is unclear whether these patients also have an increased risk of complications after elective THA or TKA. What is known rests on only 4 small studies with selected patients (Hsieh et al. 2003, Shih et al. 2004, Cohen et al. 2005, Moon et al. 2007). They indicated that cirrhosis patients—particularly those with advanced cirrhosis—have an increased risk of developing complications. However, these studies involved patients treated for various conditions, and it is unclear whether the findings also apply to patients treated for osteoarthritis. We therefore examined the risk of complications after THA or TKA for primary osteoarthritis in cirrhosis patients. We expected that the cirrhosis patients would have a higher risk of complications than patients without cirrhosis.

Patients and methods

Sources of data

We performed a historical cohort study that involved linkage of public healthcare registries with clinical databases. All 5.6

million residents of Denmark can be diagnosed and treated free of charge within the tax-funded public healthcare system. The Danish National Patient Registry (NPR) is a nationwide registry of hospital admissions since 1977 and of outpatient and emergency room visits since 1995 (Andersen et al. 1999). The data comprise relevant dates and discharge diagnoses coded in accordance with the International Classification of Diseases, edition 10 (ICD-10) since 1994 and ICD-8 before that. The Danish Hip Arthroplasty Registry (DHAR) and the Danish Knee Arthroplasty Registry (DKAR) hold data on all patients who have undergone a primary or revision THA or TKA in Denmark since January 1, 1995 (DHAR) or January 1, 1997 (DKAR) (Dansk Høftealloplastik Register 2010, Dansk Knæalloplastik Register 2010, Robertsson et al. 2010, Pedersen et al. 2012). Every public and private orthopedics department in Denmark reports to these clinical databases—which are 97% and 92% complete, respectively (Pedersen et al. 2004, 2012). The operating surgeon provides data on the indication for surgery (primary or secondary osteoarthritis, rheumatic arthritis, fracture, congenital hip dysplasia, avascular necrosis of the femoral head, or other indication), type of operation (primary or revision), type of anesthesia (general or regional), antibiotic use, prosthesis components and fixation, intraoperative complications, and revision. Individual-level data from the NPR and the DHAR/DKAR were linked through the unique personal identification number issued by the Danish Central Office of Civil Registration to all Danish citizens at birth or to immigrants. This registry also records the date of death or emigration for all Danish citizens and is continuously updated (Pedersen et al. 2006).

Study population and comorbidity

We included all Danish residents who underwent THA and TKA for primary osteoarthritis between January 1, 1995 and December 31, 2011 according to the DHAR and DKAR, and we only considered their first hip or knee arthroplasty. Those of them who had received 1 or more discharge diagnosis codes for cirrhosis (ICD-10: K70.3, K70.4, K74.6; ICD-8: 571.09, 571.92, 571.99) before the hip or knee arthroplasty were categorized as cirrhosis patients. The remaining patients were categorized as reference patients. Cirrhosis patients were further subcategorized into cirrhosis patients with clinically significant portal hypertension—defined as 1 or more diagnoses with bleeding esophagus varices (ICD-10: I85.0), gastric varices (ICD-10: I86.4), or portal hypertension (ICD-10: K76.6) before the THA or TKA—and cirrhosis patients without portal hypertension. For each cirrhosis patient and each reference patient, we identified all discharge diagnoses in the NPR from in-hospital admissions in the 5 years before the THA or TKA. Using these data, we computed the patient's Charlson comorbidity index (CCI), defined for usage with ICD-10 codes (Quan et al. 2005). Liver disease was not a comorbidity in the present study, and it was therefore excluded from the CCI.

Outcomes and statistical analysis

We computed mortality during hospitalization or within 30 days of discharge, and the risk of complications with corresponding 95% confidence intervals (CIs). Complications included intraoperative complications, transfer to an intensive care unit (ICU), transfer to a medical department, and in-hospital readmission within 30 days of hospital discharge. Using the discharge diagnosis codes shown in Table 3, we further categorized readmissions as being due to infection, liver disease, acute renal failure, venous thromboembolism, cardiovascular disease, hip dislocation, or mechanical complications—or as being due to other diagnoses. In the analysis of readmissions for hip dislocation, we included hospital contacts in outpatient clinics. We used chi-square statistics for categorical variables and Student's t-test for continuous variables to determine whether certain patient characteristics (age, gender, CCI, and number of inpatient hospitalizations in the year preceding arthroplasty) or procedural characteristics (operation site (hip or knee), type of anesthesia (regional or general), and year of operation) differed significantly between cirrhosis patients and reference patients. Logistic regression was used to compute and compare adjusted odds ratios (aORs) of all outcomes for patients with cirrhosis and for reference patients. The odds ratios were adjusted for the patient characteristics and procedural characteristics listed above. We also calculated the probability of an uncomplicated THA or TKA, i.e. the proportion of THAs or TKAs where the patients did not have any of the complications defined above. In addition, we repeated the analyses, restricting them to patients who were operated under regional anesthesia. Furthermore, we compared odds for cirrhosis patients with no clinically significant portal hypertension and for reference patients—regarding mortality during hospitalization or within 30 days of discharge, intraoperative complications, transfer to an ICU, transfer to a medical department, and readmission to hospital within 30 days of hospital discharge. Finally, we computed the cumulative incidence (i.e. risk) of deep prosthetic infection and revision in the first year after THA or TKA using competing-risk methods, with death as the competing risk (Satagopan et al. 2004), and we used competing-risk regression to adjust for the patient and procedural characteristics listed above (Fine et al. 1999). Each patient was followed from the date of THA or TKA for 1 year after this date. Deep prosthetic infection was defined by NPR diagnoses (T84.5, T84.6, and T84.7), and revisions were identified in the DHR or DKR. All statistical analyses were performed using Stata software version 12.1 and R software version 2.14.1 (R Core Team 2013).

Results

We included 363 patients with cirrhosis (59 of them with a history of clinically significant portal hypertension) and 109,159 reference patients who underwent THA or TKA for primary

Table 1. Characteristics of the patient cohort

	Cirrhosis patients	Reference patients	p-value ^a
Number of cases	363	109,159	
Median age, years	66	69	< 0.01
25th and 75th percentiles	59–71	62–76	
M/F, %	54/46	41/59	< 0.01
Hip/Knee, %	58/42	61/39	0.2
Charlson comorbidity index, %			< 0.01
0	63	82	
1	20	11	
2	8	5	
≥ 3	9	2	
Number of inpatient hospitalizations in the year before hip or knee replacement, %			< 0.01
0	53	77	
1	23	15	
2	12	5	
≥ 3	12	3	
Type of anesthesia regional/general, %	34/66	23/77	< 0.01
Year of operation	Data not shown		0.6

^a The p-value represents a comparison between the 2 groups using chi-square test or Student's t-test.

Table 2. Absolute risks (%) and adjusted odds ratios (aORs) for complications after hip or knee replacement in cirrhosis patients and reference patients

	Cirrhosis patients risk (CI)	Reference patients risk (CI)	aOR ^a (CI)
Intraoperative complications	2.48 (1.14–4.65)	1.98 (1.90–2.06)	1.3 (0.7–2.5)
Mortality within 30 days	1.38 (0.45–3.18)	0.38 (0.34–0.42)	3.9 (1.5–10)
Transfer to an intensive care unit	0.55 (0.07–1.98)	0.055 (0.042–0.072)	5.8 (1.3–25)
Transfer to a medical department	4.41 (2.54–7.06)	2.47 (2.37–2.56)	1.7 (1.0–2.9)
Readmission within 30 days	14.9 (11.4–17.0)	7.84 (7.68–8.00)	1.8 (1.3–2.4)

^a Adjusted for age, gender, Charlson comorbidity index, operation site (hip/knee), anesthesia (general/regional), and number of inpatient hospitalizations in the year preceding hip or knee replacement.

Table 3. Absolute risks (%) and odds ratios for readmission according to disease categories

Disease category, ICD-10 code	Cirrhosis patients n risk (CI)	Reference patients n risk (CI)	aOR ^b
Infection, DA ^a , DB95 ^a , DB96 ^a , DJ1 ^a , DJ9 ^a , DI0 ^a , DM00 ^a , DN30 ^a , DT814	6 1.65 (0.61–3.56)	843 0.77 (0.72–0.83)	1.8 (0.8–4.2)
Liver disease, DK7 ^a	9 2.48 (1.14–4.65)	11 0.001 (0.0005–0.01)	257 (99–672)
Acute renal failure, DN0 ^a , DN1 ^a	2 0.55 (0.07–1.98)	107 0.010 (0.008–0.011)	3.4 (0.8–14)
Venous thromboembolism, DI80 ^a , DI81 ^a , DI82 ^a , DI83 ^a , DI26 ^a	2 0.55 (0.07–1.98)	702 0.64 (0.60–0.69)	0.8 (0.2–3.2)
Cardio vascular disease, DD65, DI60–DI64, DG45, DI2 ^a	2 0.55 (0.07–1.98)	666 0.61 (0.56–0.65)	0.7 (0.2–2.9)
Hip dislocation ^c , DS73 ^a , DS83 ^a	1 0.82 (0.17–2.40)	279 0.48 (0.43–0.52)	1.5 (0.5–4.8)
Mechanical complications, DT840, DT841, DT842, DT843, DT844	7 1.93 (0.18–2.55)	1,145 1.05 (0.98–1.11)	1.7 (0.8–3.6)
Readmissions with other diagnoses, any other diagnosis	30 8.26 (5.41–11.1)	5,444 4.99 (4.86–5.12)	1.5 (1.0–2.2)

^a Any number.

^b Confounder-adjusted odds ratio (aOR) are adjusted for age, gender, CCI, operation (hip/knee), anesthesia (general/regional), and number of inpatient hospitalizations in the year preceding first hip or knee replacement.

^c Including emergency room contacts.

osteoarthritis in the period 1995–2011. Cirrhosis patients were generally younger, had male predominance, had more comorbidity, were more frequently hospitalized in the year before THA or TKA, and were more frequently under general anesthesia (Table 1). The median time from diagnosis of cirrhosis to THA or TKA was 6 years and 6 months.

The risk of intraoperative complications was similar for cirrhosis patients and for reference patients (2.48% vs. 1.98%, aOR = 1.3, CI: 0.7–2.5), whereas cirrhosis patients had higher risk of 30-day mortality (1.38% vs. 0.38%, aOR = 3.9, CI: 1.5–9.7), of transfer to an ICU (0.55% vs. 0.055%, aOR = 5.8, CI: 1.3–25), of transfer to a medical department (4.41% vs. 2.47%, aOR = 1.7, CI: 0.99–2.9), and of readmission (14.9% vs. 7.8%, aOR = 1.8, CI: 1.3–2.4) (Table 2). These aORs were essentially unaltered when we restricted our analyses to patients operated under regional anesthesia, or to the 304 cirrhosis patients with no clinically significant portal hypertension. Of the cirrhosis patients, those with clinically significant portal hypertension had higher 30-day mortality (1.7% vs. 1.3%) and risk of transfer to an ICU (1.7% vs. 0.3%) than those without any clinically significant portal hypertension. The excess risk of readmission for cirrhosis patients was due to

infection, liver disease, or acute renal failure, while there was no excess risk of cardiovascular disease or venous thromboembolism (Table 3). Cirrhosis patients had a higher 1-year risk of deep prosthetic infection than reference patients (3.1% (CI: 1.6–5.2) vs. 1.4% (CI: 1.3–1.4)), and the difference remained after adjustment for patient characteristics and procedural characteristics (adjusted subdistribution hazard ratio = 2.1, CI: 1.3–3.7). Moreover, they were more likely to require a revision arthroplasty within a year (3.7% (CI: 2.1–6.1) vs. 1.7%

(CI: 1.6–1.8)). This association remained after adjustment (adjusted subdistribution hazard ratio = 1.9, CI: 1.1–3.3). The probability of having an uncomplicated hip or knee arthroplasty was 81% (CI: 77–85) for cirrhosis patients and 90% (CI: 89.6–90.0) for reference patients.

Discussion

This nationwide registry-based historical cohort study showed that cirrhosis patients who underwent total hip or knee arthroplasty for primary osteoarthritis had a higher risk of dying, of postoperative transfer to an ICU or a medical department, of readmission, of revision, and of deep prosthetic infection than reference patients who underwent the same procedures. However, the majority (81%) of the cirrhosis patients did not have any complications and they did not have an increased risk of intraoperative complications. Cirrhosis patients had a particularly high risk of readmission for infection, liver disease, or acute renal failure.

The strengths of our study were the nationwide population-based design, the large size, and the complete follow-up in a uniform healthcare system. However, one limitation was that we did not assess the validity of our data sources. Between 1996 and 2009, the completeness of the DHR increased from 92% to 97% and the completeness of the DKR increased from 86% to 92% (Dansk Hoftealloplastik Register 2010, Dansk Knæalloplastik Register 2010). We have no reason to believe that the few unregistered procedures involved cirrhosis patients with a particularly favorable or unfavorable outcome. The validity of cirrhosis diagnoses registered in the NPR is 85% (Vestberg et al. 1997), and erroneous diagnoses would have caused us to underestimate the excess risk for cirrhosis patients. The same bias would occur if outcome data were incorrect. It is possible that surgeons are less likely to report intraoperative complications in cirrhosis patients because they accept it as normal to have some difficulty with these patients. If so, this bias might explain the lack of association between cirrhosis and intraoperative complications. All other complications were identified in independent data sources, and we believe that it would be unlikely for them to have been affected by reporting bias, although we have no validation. The validity of the mortality data originating from the Danish Central Office of Civil Registration is essentially 100% (Pedersen et al. 2006).

Another limitation of the present study was the lack of data on alcohol intake and smoking, both of which are associated with a worse outcome after elective surgery (Nath et al. 2010, Singh 2011). There is an obvious association between alcohol intake and cirrhosis, and it is likely that smoking is also more common in cirrhosis patients. Alcohol intake increases the risk of infection in cirrhosis patients (Rosa et al. 2000), but we believe that THA and TKA are mainly offered to cirrhosis patients who do not drink alcohol. Finally, the confounding effect of smoking is indirectly covered by our adjustment

for chronic obstructive pulmonary disease and cardiovascular disease. Thus, alcohol and smoking may have contributed to the association between cirrhosis and postoperative complications, but we do not believe that it fully explains it.

A final limitation of this study was the lack of detailed data on the etiology of cirrhosis and on its severity. We suspect that most of the cirrhosis patients did in fact have alcoholic cirrhosis (Sørensen et al. 2003), so we chose to report outcomes jointly for all cirrhosis patients. The patients were presumably in a compensated stage of their liver disease because the preoperative evaluation for such elective surgery would have identified and excluded patients with gross decompensation. Thus, our results indicate that even cirrhosis patients with a low perceived surgical risk have an increased risk of postoperative complications. This interpretation is supported by our finding that the cirrhosis patients with no clinically significant portal hypertension and those operated under regional anesthesia had an increased risk of postoperative complications. However, it is still meaningful to expect the risk to increase with the severity of the liver disease, in line with the previously reported higher risk according to the severity of portal hypertension (Hsieh et al. 2003, Moon et al. 2007).

Our findings agree with the results of the 4 previously published studies on cirrhosis patients who underwent THA or TKA, and 2 of them even found an increased risk of postoperative infections and acute renal failure (Hsieh et al. 2003, Cohen et al. 2005). Direct comparison is precluded by differences in indications for hip or knee arthroplasty and in patient selection. The latter difference is suggested by the markedly higher 30-day mortality estimates in the other studies (7–10% as opposed to 1.38% in the present study) (Cohen et al. 2005, Moon et al. 2007).

In other types of surgery, odds ratios for 30-day mortality for cirrhosis patients relative to population controls have ranged from 3 to 12 (Poulsen et al. 2000, Nielsen et al. 2001, Thulstrup et al. 2001, Nielsen et al. 2002, Lund et al. 2003, Arif et al. 2012), the lowest odds ratio being for transurethral resection of the prostate (Nielsen et al. 2001) and the highest being for open cholecystectomy (Thulstrup et al. 2001). So, although THA and TKA are extra-abdominal procedures performed in an elective setting, the relative increase in mortality ascribed to cirrhosis is comparable to that seen after other types of surgery. This indicates that the cirrhosis-related excess risk is a systemic problem and is not restricted to intraperitoneal procedures. However, the present study did not address the question of whether cirrhosis patients with primary osteoarthritis should or should not be offered surgery; we merely provide the basis for an informed decision.

The mechanisms behind the increased surgical risk in cirrhosis patients are the subject of debate. Circulatory instability introduced by anesthesia has been proposed (Friedman 2010), but our estimates were unaltered when we excluded patients who were operated under general anesthesia, and this clearly indicates that other mechanisms contribute. Our find-

ings rather implicate susceptibility to bacterial infections in cirrhosis patients as an important cause of their higher risk of having complications after surgery (Christou et al. 2007). In fact, a recent study of patients undergoing THA or TKA identified comorbid liver disease as the strongest predictor of deep prosthetic infection, increasing the odds 2.5-fold (Poultides et al. 2013), and prosthetic hip infections in cirrhosis patients are difficult to eradicate (Hsieh et al. 2010). Suggested mechanisms for this susceptibility include translocation of bacteria from the intestines, dysfunction of polymorphonuclear leukocytes, complement deficiency, and disturbance of the reticuloendothelial system (Møller et al. 2007). 2 studies have shown excessive activation of IL-6 and TNF- α in cirrhosis patients after surgery, and a subsequent acute-phase response (Sato et al. 1996, Lan et al. 2003); this hyperactivity offers a supplementary explanation for the increased surgical risk in cirrhosis patients. Thus, a number of different explanations for the higher surgical risk are possible, and the present study indicates that an increased susceptibility to infection is one of them—while intolerance to anesthesia is of minor importance.

In conclusion, cirrhosis patients undergoing total hip or knee arthroplasty for primary osteoarthritis have an increased risk of dying, of transfer to an ICU or a medical department, of deep prosthetic infection, of revision, and of readmission for infection, liver disease, or acute renal failure. Our results indicate that the risk applies to all cirrhosis patients and not only to severe cases. This may have implications for orthopedic surgeons' degree of preoperative awareness of even discrete signs of cirrhosis, and for the level of attention paid to liver-related problems.

TD, PJ, SO, and HV planned and designed the study. TD and PJ performed the analyses and drafted the manuscript. All the authors reviewed and approved the submitted version of the manuscript.

No competing interests declared.

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