CLINICAL GASTROENTEROLOGY AND HEPATOLOGY 2013;■:1–7

The Risk of Fractures Among Patients With Cirrhosis or Chronic Pancreatitis

Q20 ULRICH CHRISTIAN BANG,* THOMAS BENFIELD,‡,§ FLEMMING BENDTSEN,§,|| LARS HYLDSTRUP,*,§ and JENS–ERIK BECK JENSEN*,§

Q1 *Department of Endocrinology, ‡Department of Infectious Diseases, ||Department of Gastroenterology, University Hospital of Hvidovre, Hvidovre, Denmark; §Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark

Q6 **BACKGROUND & AIMS:** **Cirrhosis and chronic pancreatitis (CP) are accompanied by inflammation and malnutrition. Both conditions can have negative effects on bone metabolism and promote fractures. We evaluated the risk of fractures among patients with CP or cirrhosis and determined the effect of fat malabsorption on fracture risk among patients with CP.**

METHODS: **We performed a retrospective cohort study using the Danish National Patient Register to identify patients diagnosed with CP or cirrhosis. We analyzed data collected from January 1, 1995, to December 31, 2010, on 20,769 patients (35.5% female) with cirrhosis and 11,972 patients (33.5% females) with CP. Each patient was compared with 10 age- and sex-matched controls. We also assessed the risk of fractures among patients with CP who received pancreatic enzyme substitution (PES) for fat malabsorption.**

Q7

RESULTS: **During the study period, bone fractures occurred in 3954 patients with cirrhosis and 2594 patients with CP. The adjusted hazard ratio (HR) for any fracture was 2.4 in patients with cirrhosis (95% confidence interval [CI], 2.2–2.5) and 1.7 in patients with CP (95% CI, 1.6−1.8). The relative risk of low-trauma fractures was highest among individuals younger than 50 years old. Alcohol as an etiology was associated with an increased risk of fracture compared with patients with nonalcoholic cirrhosis (HR, 2.4 vs 1.5; $P < .0001$) and CP (HR, 2.0 vs 1.5; $P < .0001$). Patients with CP receiving PES for fat malabsorption had a lower risk of fractures than other CP patients (HR, 0.8; 95% CI, 0.7–0.9). However, increasing the duration of treatment with PES was associated with an increased risk of fracture.**

CONCLUSIONS: **Patients, especially younger patients, with cirrhosis or CP have an increased risk of fractures of all types.**

Keywords: Liver Disease; Fibrosis; Orthopedic; Database Analysis.

Q8 Q9 Q10 Several diseases in the gastrointestinal tract and the liver are accompanied by comorbidities as a result of malnutrition and an increased systemic inflammatory state. Examples of such diseases are cirrhosis and chronic pancreatitis (CP). Both diseases bring the body into an increased inflammatory state with Q11 changes in the cellular compartments of the immune system.[1,2] This may exert deleterious effects on bones because bone turnover depends on the dynamic equilibrium between the proinflammatory and anti-inflammatory pathways. In addition, when taking into account the increased prevalence of general malnutrition in patients with cirrhosis or CP, it becomes clear that it is a demanding task to preserve healthy bones in these patients.[3,4]

The Danish National Patient Register offers a unique opportunity for identifying patients with specific diseases. It was our aim to evaluate the incidence of fractures including low-trauma fractures among patients with cirrhosis and CP, and to analyze the impact of alcohol as an etiology on the incidence of fractures. Furthermore, we wanted to assess the effect of pancreatic enzyme substitution (PES) on fracture incidence in patients with CP.

Methods

Study Population

We performed a retrospective cohort study using Danish nationwide registries. Patients diagnosed with cirrhosis or CP were identified from the Danish National Patient Register, which contains discharge diagnoses on all inpatient (since 1977) and outpatient admissions (since 1995).[5] Information was retrieved for the period from January 1, 1995, to December 31, 2010. Patients were included if they had been discharged with one of the following International Classification of Diseases, 10th edition codes: K86.0 (alcohol induced CP), K86.1 (other CP), K70.2

Abbreviations used in this paper: BMD, bone mineral density; CI, confidence interval; CP, chronic pancreatitis; CPD, chronic pulmonary disease; HR, hazard ratio; IR, incidence ratio; PBC, primary biliary cirrhosis; PES, pancreatic enzymes substitution; PY, person-years; RANK, receptor activator of nuclear factor-κB.

1542-3565/$36.00
http://dx.doi.org/10.1016/j.cgh.2013.04.031

(alcoholic fibrosis and sclerosis of liver), K70.3 (alcoholic cirrhosis), K74.3 (primary biliary cirrhosis), K74.4 (secondary biliary cirrhosis), K74.5 (biliary cirrhosis, unspecified), K75.4 (autoimmune hepatitis), and K75.8 (other specified inflammatory liver disease). Viral cirrhosis was not included in this analysis.

Controls

For each patient we retrieved 10 age- and sex-matched controls using the Danish Civil Registration System. The Danish Civil Registration System tracks changes in vital status, including date of emigration and date of death for the entire Danish population, and no persons are lost to follow-up evaluation.[6] Each control was assigned a cohort entry date identical to the matching case's entry date.

Outcome Variable

For both cases and controls, an event was defined as any fracture that happened in the period from January 1, 1995, to December 31, 2010. Fractures were identified using the following International Classification of Diseases, 10th edition codes: S02 (skull and facial bones), S12 (cervical spine), S22.0/1/2 (thoracic spine), S22.3/4 (ribs), S32.1/2/3/4/5/7/8 (pelvis), S32.2 (lumbar spine), S42.0/1/7/8/9 (shoulder), S42.2/3/4 (humerus), S52.0/1/2/3/4/7/9 (upper forearm), S52.5/6/8 (lower forearm), S62 (wrist and hand), S72.0/1/2 (proximal femur), S72.3/4/7/8/9 (lower femur), S82 (lower leg, ankle), S92 (foot), and, finally, M80.1/2/3/4/5/8/9 (osteoporotic fracture). We classified fractures of the spine, humerus, distal forearm, and proximal femur as low-trauma osteoporotic fractures.[7,8]

Covariates

We registered the diagnosis of osteoporosis (M80.0–M81.9) and dependency of alcohol (F10.1–2). As a marker of smoking we used the diagnosis of chronic pulmonary disease (CPD) (J40–J47, J60–J67). We retrieved birth dates, sex, and socioeconomic status from the Danish Civil Registration System. These covariates were used as categoric data.

Fat Malabsorption

We wanted to evaluate the impact of fat malabsorption on the risk of fractures in patients with CP. We identified the patients who had redeemed at least one prescription of PES through the Danish Prescription Database.[9] Reimbursement for expenses related to PES is available only to patients who have been examined and diagnosed with fat malabsorption by an exocrine function test, fecal elastase test, or fecal fat test. Hence, the redemption of PES can be used to identify patients with fat malabsorption, and we compared fracture rate in these patients with the part of our CP cohort not registered with PES prescriptions. We estimated the cumulative exposure to PES by dividing the total reimbursed prescriptions of PES in defined daily doses during the follow-up period with the follow-up time for each particular patient (ie, 50 daily doses during a follow-up time of 250 days would yield an exposure of 20%). We then classified the patients into the following groups depending on their exposure to PES: no exposure, less than 25% of the follow-up period, 25%–50% of the follow-up period, 50%–100% of the follow-up period, and, finally, consumption of more than the recommended doses during the whole follow-up time as more than 100% of the follow-up period.

Statistics

Baseline characteristics were presented as means or medians. Risk time was expressed in person-years (PY) and defined as the time from diagnosis of cirrhosis or CP until the occurrence of an event: death or end of follow-up period. Fractures were reported as incidence rates (IR) in numbers per Q12 1000 PY. The risk time was split into decades of lifetime to adjust for age-dependent covariates. We used univariate and multivariate Cox proportional hazard models to assess the hazard ratio (HR) with 95% confidence interval (CI). Persons with missing data were excluded from the analyses. We used the statistical software SAS 9.2 (SAS Institute, Inc, Cary, NC). The study was approved by the Danish Health and Medicines Authority and followed the regulations set up by the Danish Data Protection Agency.

Results

The cohort consisted of 360,151 persons with a total of 41,666 fractures during 2,310,187 PY. Cirrhosis was diagnosed in 20,769 patients (35.5% females) with a mean age of 56.6 years (SD, 11 y) at cohort entry. CP was diagnosed in 11,972 patients (33.5% females), with a mean age of 54.5 years (SD, 14 y). The median follow-up time was 1.7 years (Q1–Q3, 0.3–4.3 y) for patients with cirrhosis and 3.9 years (Q1–Q3, 1.2–8.1 y) for patients with CP. Demographic details are presented in Table 1.

Fractures in Patients With Cirrhosis

The unadjusted incidence rate of any fracture was 64.5 (95% CI, 62.5–66.5) per 1000 PY among patients with cirrhosis

Table 1. Demographics at Start of Follow-Up Evaluation

	Cirrhosis (n = 20,769)	Controls (n = 207,690)	*P* value	CP (n = 11,972)	Controls (n = 119,720)	*P* value
Females, %	35.5	35.5		33.5	33.5	
Mean age (SD), y	56.6 (11)	56.6 (11)		54.5 (14)	54.5 (14)	
Etiology, % alcoholic	89.5	-		52.7		
Social status, % working	18.3	56.4	<.0001	30.0	57.4	<.0001
Unemployed/retired	70.0	39.3		63.1	38.2	
Other	11.8	4.3		8.9	4.4	
Osteoporosis, %	6.9	3.7	<.0001	7.5	3.4	<.0001
Alcohol abuse, %	49.5	2.5	<.0001	30.5	2.3	<.0001
CPD, %	13.9	8.0	<.0001	18.3	7.7	<.0001

NOTE. Demographic characteristics of patients with cirrhosis, CP, and age- and sex-matched controls. Q13