



# Comparison of fracture risk between patients with ileal pouch-anal anastomosis for ulcerative colitis and the general population



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## KEYWORDS

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Ileal pouch-anal  
anastomosis;  
Bone metabolism;  
Fracture risk

## Abstract

**Background:** Restorative proctocolectomy with *ileal pouch-anal anastomosis* (IPAA) is the preferred surgical treatment for *ulcerative colitis* (UC). Little is known of how the operation affects bone metabolism and fracture risk. The aim of this retrospective cohort study was to investigate fracture risk and serum markers of bone metabolism following IPAA in a national cohort of Danish UC patients.

**Methods:** Diagnostic codes for 1757 patients and 8785 controls were obtained from the National Patient Register while blood results were collected from a regional database. Postoperative fracture free survival was evaluated on a Kaplan–Meier plot. Fracture hazard ratios (HR) after IPAA were calculated from Cox proportional hazards regression analysis.

**Results:** Fracture risk after IPAA was significantly reduced (adjusted HR = 0.49, 95% CI: 0.43; 0.55,  $p < 0.001$ ). Prior fractures and alcoholism independently increased fracture risk significantly. Osteoporotic fracture risk after IPAA was reduced, significantly for wrist fractures (aHR = 0.39, 95% CI: 0.22; 0.71,  $p = 0.002$ ), and borderline insignificantly for spine fractures (aHR = 0.51, 95% CI: 0.26; 1.01,  $p = 0.054$ ). Vitamin D and calcium levels were significantly higher in the patient group (61.2 nmol/L vs. 58.9 nmol/L,  $p = 0.04$  and 1.24 mmol/L vs. 1.21 mmol/L,  $p < 0.01$ , respectively), while parathyroid hormone and phosphate levels were significantly lower (4.9 pmol/L vs. 6.2 pmol/L,  $p < 0.01$  and 1.08 mmol/L vs. 1.12 mmol/L,  $p < 0.01$ , respectively).

**Conclusion:** Fracture risk after IPAA is significantly reduced compared to the general population. Prospective studies are needed to verify the biochemical results.

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## 1. Introduction

The risk of sustaining fractures for patients with *ulcerative colitis* (UC) is indiscriminately of disease management similar to that of the general population.<sup>1–3</sup>

Bowel surgery as a whole has not been found to independently affect fracture risk in UC,<sup>1,3,4</sup> albeit no study has evaluated fracture risk after restorative proctocolectomy with *ileal pouch-anal anastomosis* (IPAA), which is the surgical treatment of choice for patients with intractable UC.

Data from cross-sectional and prospective studies on bone metabolic disturbances suggestive of fracture risk changes following IPAA are scarce,<sup>5–9</sup> and the studies have all focused on absorptiometric and biochemical measures of bone disease, the clinical significance of which remains unclear.

Fracture risk is the clinically most important surrogate measure of bone disease, and detection of demographic groups in high risk of fractures is important, considering the enormous personal and socio-economic costs of fractures and the high mortality associated with especially osteoporotic fractures.<sup>10–12</sup>

The aim of this retrospective, population-based, national cohort study was to evaluate fracture risk and biochemical variables associated with bone metabolism in Danish UC patients following IPAA.

## 2. Materials and methods

### 2.1. Patients and controls

All Danish IPAA patients operated for UC in the period 1980–2010 ( $n = 1757$ ) have been identified in a previous study (Colorectal Disease, Manuscript ID CDI-00769-2012). The average temporal dissociation between the UC diagnosis (Appendix A) and IPAA in this cohort was  $4.2 \pm 4.9$  years.

An age- and gender matched control group of 8785 individuals was selected from the Danish Civil Registration System (CRS). The Civil Registration number is a unique 10 digit code given to all Danish citizens at birth or upon attaining citizenship and consists of the date of birth (date–month–year) and four additional digits, e.g. "010101-0001" for a person born January 1st 2001. Each patient was age- and gender matched to five controls, all of whom were assigned an "index date of IPAA surgery" corresponding to the date of IPAA surgery for their respective patient. If the IPAA procedure was performed in multiple stages, the "date of IPAA" was defined as the first surgical procedure.

The inclusion criterion for the control group was that each individual had to be alive and living in Denmark on the date of the IPAA operation of their respective patient in order to approximate a sufficient number of person–years when comparing fracture risk and fracture free survival.

### 2.2. Outcome variables

#### 2.2.1. Fractures

Fracture diagnoses for both patients and controls were obtained from the Danish National Patient Register (NPR)

and included fractures of the femur, foot, hip, humerus, patella, pelvis, radius, ulna, ribs, tibia, fibula, vertebrae/spine, wrist and others (Appendix A). In accordance with generally accepted definitions, we defined fractures of the spine, wrist, and hip as osteoporotic in nature.<sup>13</sup>

The NPR is a computer-based register founded in 1977, where all non-psychiatric contacts with the health care system are registered with an individual's Civil Registration number, including information on residency and death. The completeness of the NPR combined with linkage possibilities to other registers via the Civil Registration number makes the register unique and provides the basis for high quality epidemiological research in Denmark.<sup>14</sup> The validity of fracture diagnoses in Danish IBD patients is high, previously estimated at 97%.<sup>2</sup>

#### 2.2.2. Biochemistry

Blood tests were drawn from the Department of Biochemistry, Aarhus University Hospital, where all biochemical results from the Region of Central Denmark have been filed since 1992. 25-OH-Vitamin D (25OHD), parathyroid hormone (PTH), ionized calcium, phosphate, alkaline phosphatase, alanine transaminase (ALT), and creatinine levels, were evaluated where available. The Department of Biochemistry is an *International Organization for Standardization* (ISO) 9000 certified laboratory.

#### 2.2.3. Follow-up

The study period was stratified in two periods: Time before IPAA (i.e. from 1977–IPAA), and time after IPAA. Patients and controls were censored from follow-up of "fracture free survival" after the index date when they sustained a fracture, died or at the end of the study period (September 2012).

#### 2.2.4. Statistical analysis

Normally-distributed data were summarized with means and standard deviations, and p-values were found using Student's paired t-test. For differences in categorical variables between the patient and control group, chi-squared test was used to compute p-values. Cox proportional hazards regression analysis was used in uni- and multivariate analysis of the relationship between specific clinical characteristics (IPAA, chronic alcohol abuse, prior fractures, disease duration, surgery for pouch dysfunction and the Charlson Comorbidity Index<sup>15</sup>) and fracture risk. Odds ratios (OR), hazard ratios (HR) and adjusted hazard ratios (aHR) were calculated to estimate fracture risk. Difference in fracture free survival after the index date was illustrated on a Kaplan–Meier plot. A p-value < 0.05 was considered statistically significant.

## 3. Ethical considerations

Permission to analyze sensitive personal information in this study was given by the Danish Data Protection Agency under journal number 2012-58-0006, and the study was approved by the regional legal department.

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