Risk Factors for Osteoporosis in Patients with Ulcerative Colitis Following Restorative Proctocolectomy

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Introduction: This study was performed to assess the prevalence and risk factors for osteoporosis in postoperative ulcerative colitis (UC) patients after restorative proctocolectomy. **Patients and Methods:** A total of 58 consecutive postoperative UC patients were selected from our institute. Patients underwent total proctocolectomy and ileal pouch-anal anastomosis (IAA) or ileal pouch-anal canal anastomosis (IACA) between 1998 and 2006. Bone mineral density (BMD) (g/cm²) of the lumbar spine or femoral neck was measured by dual energy X-ray absorptiometry (DXA). Corticosteroid-induced osteoporosis was defined as a lumbar spine or femoral neck T-score of -2.0. **Results:** Osteoporosis was observed in 24 (41%) of 58 postoperative UC patients over a median postoperative follow-up period of 4.3 ± 2.3 years. The factors associated with osteoporosis were female over 50 years old and postoperative corticosteroid use. Bone fractures were documented in three patients in the osteoporosis group. The change in T-score with 1 to 2 years of bisphosphonate therapy was $+0.6 \pm 0.86$. **Conclusions:** The prevalence rate of osteoporosis was 41%, even after a median of 4.3 years after colectomy with IAA or IACA. Osteoporosis was associated with two risk factors (female over age 50 years and corticosteroid use). After receiving appropriate drug therapy, the BMD values of osteoporosis patients approached normal levels.

Key Words: ulcerative colitis, osteoporosis, proctocolectomy

Introduction

Corticosteroid therapy has been used for the treatment of ulcerative colitis (UC), but it has a number of side effects, including osteoporosis, mental disorders, myopathy, infection, and glucose intolerance. The overall prevalence of osteopenia and osteoporosis in inflammatory bowel disease (IBD) is approximately 15%[1]. In a peripheral Dutch hospital study performed in 2008, 168 IBD patients underwent dual energy X-ray absorptiometry (DXA)[2]. Low bone mineral density (BMD) with a T-score < -1 was observed in 64.3% of cases, and osteoporosis with a T-score < -2.5 was found in 23.8%. In a population-based study performed in 83 UC patients undergoing DXA in Western Sweden in 2009, decreased BMD with a Z-score < -1 SD occurred in 47.0% of cases and low BMD with a Z-score < -2

SD was observed in 24.1%[3]. Reported risk factors for reduced BMD in 144 patients with IBD were poor calcium intake, low body mass index (BMI), advanced age, and use of azathioprine[3~8].

Patients in whom restorative proctocolectomy and ileal pouch-anal anastomosis (IAA) or ileal pouch-anal canal anastomosis (IACA) are indicated have usually been treated with corticosteroids, including corticosteroid pulse therapy. Reports of bone disorders in postoperative UC patients are rare. The present study was performed to assess the prevalence and risk factors of osteoporosis in postoperative UC patients after restorative proctocolectomy and IAA or IACA.

Patients and Methods

Fifty-eight consecutive postoperative UC patients were selected from among those treated at

Table 1 Comparison of demographic and general clinical data between the osteoporosis and normal BMD groups measured at the time of study enrolment

Variable	Osteoporosis T-score ≤ -2.0 24 (41%)	Normal T-score >2.0 34 (59%)	p value
Age (years)	45.5 ± 18.8	30.5 ± 9.9	0.125
Female sex	13 (54%)	12 (35%)	0.15
Female >50 years old	11 (46%)	6 (18%)	0.020
BMI	21.2 ± 2.6	20.9 ± 4.1	0.801
History of bone fracture	3 (13%)	0	0.034
Postoperative follow-up period (years)	3.0 ± 1.7	5.0 ± 2.6	0.073
Postoperative corticosteroid use	10 (42%)	6 (18%)	0.044

BMI: body mass index.

our institute. They underwent restorative proctocolectomy and IAA or IACA between 1998 and 2006. The study population consisted of 33 men and 25 women with an average age of 42.4 (range 18–82) years. The operative indications were refractory disease in 35 cases (60%), bleeding in 12 cases (21%), dysplasia or cancer in 9 cases (16%), and perforation in 2 cases (3%). The clinical variables were compared between patients with osteoporosis and those with normal BMD. A retrospective review comparing BMD before and after bisphosphonate therapy was also performed in 9 patients with osteoporosis. The effectiveness of drug therapy for osteoporosis was measured. All patients gave informed consent, and the study was performed in accordance with the Declaration of Helsinki.

Bone mineral density

The BMD (g/cm²) of the lumbar spine or femoral neck for patients with bone fractures was measured by DXA. The T-score is defined as the number of standard deviations (SD) by which a given BMD measurement exceeds or falls below the normal mean BMD of healthy 30-year-old individuals (peak bone mass). Corticosteroid-induced osteoporosis was defined as a lumbar spine or femoral neck T-score below -2.0.

Definitions of variables

The variables studied were classified as either: (1) variables that were measured at the time of enrollment in the study and reflect post-IAA or post-IACA information, including age, female sex, female over age 50 years, BMI, history of bone fracture, and postoperative corticosteroid use; and (2) vari-

ables the values of which were known or measured at the time of restorative proctocolectomy and IAA or IACA, including age at diagnosis, age at operation, number of years between diagnosis and operation, operative indication(s), and preoperative total corticosteroid dosage.

Statistical analysis

A case-control study was performed with cases including patients with osteoporosis. The data were analyzed using the PASW statistical package (PASW Statistics, version 17.0; SPSS, Chicago, IL). Univariate associations between bone mass categories and categorical study variables were assessed using the χ^2 test, the Mann–Whitney test, or Student's t test. In all analyses, $p < 0.05$ was taken to indicate statistical significance.

Results

Osteoporosis was observed postoperatively in 24 (41%) of 58 UC patients with a median postoperative follow-up time of 4.3 ± 2.3 years. Based on the results of univariate analysis, the factors that were shown to be associated with increased risk of osteoporosis were female over 50 years old and postoperative corticosteroid use (Table 1). Age, BMI, and postoperative period were not significantly associated with osteoporosis risk (Table 1). At the times of restorative proctocolectomy and IAA or IACA, there were no significant differences in clinical data between the osteoporosis and normal BMD groups (Table 2).

Bone complications (lumbar spine fractures) were documented in 3 (13%) of 24 patients in the osteoporosis group (p = 0.034) (Table 1), with T-scores rang-

Table 2 Comparison of demographic and general clinical data between the osteoporosis and normal BMD groups at the time of restorative proctocolectomy and IAA or IACA

Variable	Osteoporosis T-score≤−2.0 24 (41%)	Normal T-score>2.0 34 (59%)	p value
Age at diagnosis (years)	31.0 ± 17.6	28.1 ± 10.8	0.194
Age at operation (years)	42.0 ± 19.7	35.0 ± 10.2	0.089
Years from diagnosis to operation	10.0 ± 7.9	6.6 ± 6.1	0.069
Operative indication			0.539
Refractory	15 (63%)	20 (59%)	
Cancer or dysplasia	5 (21%)	4 (12%)	
Bleeding	3 (13%)	9 (26%)	
Perforation	1 (4%)	1 (3%)	
Preoperative corticosteroid total dosage			0.531
None	0	0	
<10 g	8 (36%)	13 (48%)	
10-20 g	6 (27%)	8 (30%)	
>20 g	8 (36%)	6 (22%)	

Table 3 Cases that developed bone fractures

Age (years)	Sex	BMI	Postoperative corticosteroid use	T-score (SD)	Bone fracture
71	female	23.8	+	−3.9	spine
65	male	19.1	+	−2.7	spine
24	male	13.8	−	−3	spine

SD: standard deviation.

Table 4 Presence of osteoporosis by years since operation

	Years since operation		
	≤3	4-6	≥7
Osteoporosis ratio	12/24	8/21	3/0
	50%	38%	30%

Table 5 Changes in T-score by drug therapy with bisphosphonate, vitamin D, and calcium

	Before drug therapy	After drug therapy	Changes
T-score (n = 9)	−2.60 ± −0.3	−1.4 ± 1.13	0.6 ± 0.86

ing from −2.7 to −3.9 (Table 3). After restorative proctocolectomy and IAA or IACA, two patients required corticosteroid treatment for residual proctitis.

The osteoporosis ratio decreased with number of years between diagnosis and operation (Table 4). The osteoporosis ratio was 50% for less than 3 years from restorative proctocolectomy and IAA or IACA, while the value was 30% at more than 7 years.

A difference in T-score (0.6 ± 0.86) was observed after 1 to 2 years of bisphosphonate therapy (Table 5). The T-score was normalized in 5 (56%) of 9 patients.

Discussion

Patients who underwent restorative proctocolectomy and IAA or IACA had already undergone corticosteroid therapy, including corticosteroid pulse therapy. Overall, 41% of patients undergoing restorative proctocolectomy and IAA or IACA had osteoporosis in our institute, which is a greater percentage than previously reported for IBD patients[2]~[10]. Most cases were not treated for osteoporosis. Thus, patients who underwent restorative proctocolectomy and IAA or IACA had been on long-term high-dose corticosteroid therapy. Other reasons may be continuing malnutrition and chronic inflammation.

In the present study, the risk factors for postop-

erative osteoporosis in UC patients were female over age 50 years and corticosteroid usage. The risk factor of female over age 50 years may be related to the effects of estrogen. In most cases, postoperative corticosteroid usage was due to pouchitis or residual proctitis and anadrenalism. The patients with bone fractures consisted of two men and one woman. Thus, it should be influenced not only by female over age 50 years but also by corticosteroid usage.

In this study, bone fractures occurred at the lumbar spine, and all cases occurred in patients with osteoporosis. This was compatible with the suggestion that the most fragile site in patients with corticosteroid-induced osteoporosis is the spine. The risk of fragility fractures was higher in the osteoporosis group than in the normal BMD group.

BMD changed after the operation. The number of cases with osteoporosis decreased with longer follow-up. Restorative proctocolectomy with IAA or IACA has been reported to have a beneficial effect on BMD in UC patients[11][12]. There may be a positive correlation between the increase in BMD and the time since the operation[11], which may be due to removal of the colon, better nutrition, and discontinuation of corticosteroids.

The Japanese Society for Bone and Mineral Research has produced guidelines for treatment of osteoporosis with corticosteroid usage; treatment of osteoporosis was recommended for patients using or planning to use oral glucocorticoids for 3 months or longer, and also those with prior fragility fractures or new fractures during treatment, or % YAM (Young Adult Mean) < 80, or prednisolone equivalent > 5 mg/day[13]. It was suggested that bisphosphonates for the treatment of osteoporosis as the first choice. In this study, bisphosphonate improved BMD and changed the osteoporosis ratio. Active treatment is needed for UC patients with osteoporosis. However, this is difficult for young women of childbearing age because of the potential adverse effects on the fetus.

The findings of the present study have several implications. UC patients may be considered a high-risk group for bone loss, even after restorative proc-tocolectomy with IAA or IACA, and a base DXA test may be needed for follow-up after the operation. In addition, close monitoring of BMD may be necessary in patients at risk, such as females over the age of 50 years and those on corticosteroids. Proper surveillance of patients at risk could result in early diagnosis and therapeutic intervention.

Conclusions

In the present study, the prevalence of osteoporosis was 41%, even at a median of 4.3 years after proctocolectomy with IAA or IACA. Osteoporosis was associated with two risk factors: female over age 50 years and corticosteroid use. Bisphosphonate therapy given to osteoporosis patients resulted in normalization of BMD in most cases.

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大腸全摘術を施行した潰瘍性大腸炎症例における骨粗鬆症の危険因子

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〔目的〕大腸全摘を施行した潰瘍性大腸炎症例における骨粗鬆症の有病率や骨粗鬆症の危険因子について検討を行った．〔対象および方法〕当科における潰瘍性大腸炎58症例を対象とした．1998年から2006年までの大腸全摘および回腸嚢肛門吻合もしくは回腸嚢肛門管吻合を施行した．腰椎または大腿骨頸部の骨密度BMD（g/cm²）をdual energy X-ray absorptiometry（DXA）を用いて測定した．骨粗鬆症はT-score-2.0を基準とした．〔結果〕骨粗鬆症は術後観察中央期間4.3±2.3年中58症例中24例（41％）に認めた．骨粗鬆症の危険因子は50歳以上の女性と術後のステロイド投与であった．骨折は骨粗鬆症症例の3例に認めた．1年から2年間のビスフォスフォネート剤の投与によりT-scoreは＋0.6±0.86変化した．〔結語〕骨粗鬆症は，大腸全摘および回腸嚢肛門吻合もしくは回腸嚢肛門管吻合後の観察中央期間4.3年で，58症例中24例（41％）に認めた．骨粗鬆症は2つの危険因子（50歳以上の女性とステロイド投与）に関連していた．骨粗鬆症症例に対する薬物療法により，BMDは正常域へ改善した．