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Original article

Risk factors for decreased bone mineral density in inflammatory bowel disease: A cross-sectional study

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SUMMARY

Background & aim: Although inflammatory bowel disease (IBD) patients are at risk for metabolic bone disease, studies analyzing this correlation have identified various risk factors, including disease phenotype, age, sex and steroid therapy. Furthermore, few studies have assessed risk factors for bone loss in Japanese IBD patients. This study analyzed risk factors for metabolic bone disease in Japanese IBD patients.

Methods: This cross-sectional study assessed 388 patients with IBD aged 20–50 years, including 232 with ulcerative colitis (UC) and 156 with Crohn's disease (CD). Bone mineral density of the femoral neck, total femur and lumbar spine was quantified by dual-energy X-ray absorptiometry. The blood concentrations of bone metabolism markers were measured. History of smoking and bone fracture, and nutritional intake were assessed using questionnaires.

Results: Of the 388 patients with IBD, 78 (20.1%; UC, 17.2%; CD, 24.4%) had osteopenia and 17 (4.4%; UC, 3.4%; CD, 5.8%) had osteoporosis, as assessed by T-score. Bone mineral density of the lumbar vertebrae was lower in males than in females. Multivariate regression analysis showed that risk factors for bone loss in UC patients were male sex, low body mass index (BMI), high steroid dose and disease location. Risk factors for bone loss in CD patients were male sex and low BMI.

Conclusion: Among Japanese patients with IBD, male sex and low BMI were associated with increased risk for metabolic bone disease. In addition, Steroid therapy shouldn't be indiscriminate in UC patients. These findings may help identify patients at particularly high risk of metabolic bone disease and may help implement appropriate therapies in a timely manner and improve long-term quality of life.

1. Introduction

Metabolic bone diseases such as osteopenia and osteoporosis increase the risk of bone fracture and negatively affect quality of life and independent living in aging individuals. Patients with inflammatory bowel disease (IBD), including ulcerative colitis (UC) and Crohn's disease (CD), have been shown to be at increased risk of metabolic bone disease [1–3]. Factors associated with the pathogenesis of osteoporosis in patients with IBD include age [4,5], female sex [6], menopausal status in women, treatment with corticosteroids [7,8], malnutrition, calcium and vitamin D

Abbreviations: BMI, body mass index; BMD, bone mineral density; CD, Crohn's disease; CDAI, Crohn's disease activity index; CI, confidence interval; CRP, C-reactive protein; DEXA, dual-energy X-ray absorptiometry; IBD, inflammatory bowel disease; IL, interleukin; NTX, amino-terminal collagen type-I telopeptide; TNF, tumor necrosis factor; UC, ulcerative colitis; YAM, young adult mean.

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deficiency, immobilization, low body mass index (BMI) [9], smoking and hypogonadism [10]. In addition, inflammatory agents that affect the intestinal immune system in IBD [11,12], including the proinflammatory cytokine tumor necrosis factor (TNF)-α and factors belonging to the receptor activator for nuclear factor κB ligand (RANKL)/osteoprotegerin system, have been reported to enhance bone resorption [10,13]. However, the prevalence of osteoporosis and osteopenia in IBD patients varies among studies, as do the reported risk factors. Thus, the pathogenesis of metabolic bone disease in IBD patients is multifactorial, complex, and only partly understood.

Most studies on the risk of bone disease in IBD have involved western patients. To date, however, few studies have fully investigated the risk of bone disease in Japanese patients with IBD. Data from Western populations cannot be extrapolated to Asian populations, due to differences in genetic background, environmental factors including dietary habits and the use of biologic agents. This study evaluated the prevalence of osteoporosis and osteopenia and assessed the risk factors for bone loss in 388 Japanese IBD patients.

2. Methods

2.1. Patients and study design

Of the 395 patients originally enrolled, seven were excluded because of pregnancy or poor compliance with the study protocol. This study involved 388 Japanese patients aged 20–50 years with IBD, including 232 with UC and 156 with CD, who were treated at Keio University Hospital in Japan for two years from 2009 to 2010. Pregnant and menopausal women were excluded. UC and CD were diagnosed based on clinical, endoscopic, radiographic, and histopathologic criteria. Patient characteristics were obtained from medical records, interviews and questionnaires. This study conformed to the Declaration of Helsinki, and the protocol was approved by the Ethics Committee at Keio University School of Medicine. Patients provided written informed consent. All data were analyzed anonymously.

In this cross-sectional study, bone mineral density (BMD), biochemical variables and bone metabolism markers were each measured once, at the same visit. Disease history and dietary/lifestyle characteristics were recorded using questionnaires.

2.2. Bone density and biochemical measurements

BMDs of the lumbar spine (L2–L4), left femoral neck and total femur were measured by dual-energy X-ray absorptiometry (DEXA; Prodigy, GE Healthcare, Chalfont, UK) at Keio University Hospital. BMD was reported as g/cm^2 and as T and Z scores, which were calculated as the number of standard deviations (SD) relative to young normal and age-matched healthy controls, respectively. Low BMD was defined by World Health Organization criteria [14,15]. T scores greater than −1 SD were categorized as normal, whereas T scores from −1.0 to −2.5 SD and less than −2.5 SD were categorized as diagnostic for osteopenia and osteoporosis, respectively. Absolute BMDs (g/cm^2) of the lumbar spine and femoral neck were also expressed as being above and below the mean and 1 SD.

In Japan, the diagnostic criteria for osteoporosis are less than 70% of the young adult mean (YAM) or 70–80% of the YAM and a history of osteoporotic fractures [16].

Blood samples were collected on the same day as DEXA was performed. Serum markers measured at SRL Inc. (Tokyo, Japan) included amino-terminal collagen type-I telopeptide (NTX) (normal range: 9.5–17.7 nmol BCE/L in males and 7.5–16.5 nmol BCE/L in females), bone alkaline phosphatase (BAP) (normal range: 3.7–20.9 μg/L in males and 2.9–14.5 μg/L in females), calcium (normal range: 8.5–10.2 mg/L), parathyroid hormone (normal range: 10–65 pg/mL), vitamin D (normal range: 20.0–60.0 pg/mL), TNF-α and IL-1β. Other serological markers, including C-reactive protein (CRP), total protein, albumin, total cholesterol, hemoglobin and phosphorus, were measured at Keio University. Table 2 shows patient biochemical characteristics at baseline. NTX and BAP were markers of bone metabolism, and TNF-α, IL-1β and CRP were markers for inflammation.

2.3. Questionnaires and clinical records

Information collected from questionnaires and medical records included treatments for IBD and bone disease; total steroid dose; disease location; history of surgery, hospitalization and disease; coexisting medical conditions; disease duration; and height, weight, past treatment for bone disease, and disease activity. In addition, the Lichtiger clinical activity index [17] was measured in

Table 1
Patient demographic and clinical characteristics.

	UC	CD	Total
Number	232	156	388
Sex (M/F)	112/120	110/46	222/166
Age (yr)	36.1 ± 7.8 (20.0–50.0)	35.5 ± 8.1 (20.0–50.0)	35.9 ± 8.0 (20.0–50.0)
Disease duration (yr)	9.77 ± 7.28 (0.27–39.83)	11.90 ± 7.82 (0.08–34.82)	10.62 ± 7.56 (0.08–39.83)
BMI (kg/m^2)	21.0 ± 3.2 (14.8–34.9)	21.2 ± 3.7 (12.2–34.4)	21.0 ± 3.4 (12.2–34.9)
Body weight (kg)	57.50 ± 11.64 (37.0–100.0)	60.02 ± 13.27 (30.0–112.0)	58.51 ± 12.37 (30.0–112.0)
Height (cm)	165.1 ± 8.17 (140.7–183.4)	168.0 ± 8.95 (142.6–186.0)	166.3 ± 8.60 (140.7–186.0)
Disease location (%)	Total/left/right/rectum/colectomy	Small intestine/Colon/both	
	55.2/30.6/0.9/9.0/4.3	10.3/26.3/63.4	
Number of operations	0.07 ± 0.25 (0–1)	1.19 ± 1.46 (0–7)	0.52 ± 1.13 (0–7)
Total steroid dose (g)	8.0 ± 16.3 (0.0–198.3)	6.7 ± 12.8 (0.0–72.2)	7.5 ± 15.0 (0.0–198.3)
Disease activity	CAI	CDAI	
	3.1 ± 2.9 (0–15)	97.2 ± 78.5 (−30.92–363.72)	
Past treatment for bone disease (number)	Sodium risedronate hydrate/alfacalcidol	Sodium risedronate hydrate/alfacalcidol	Sodium risedronate hydrate/alfacalcidol
	4/0	1/1	5/1
Number of hospitalizations	1.6 ± 2.0 (0–12)	3.8 ± 3.4 (0–19)	2.5 ± 2.8 (0–19)
History of fracture (yes)	64 (27.6%)	38 (24.4%)	102 (26.3%)
Previous or current smoker (yes)	83 (35.8%)	67 (42.9%)	150 (38.7%)
Number of cigarettes/day	1.1 ± 4.2 (0–40)	2.2 ± 5.6 (0–30)	1.6 ± 4.8 (0–40)

Data are means ± standard deviation (range), or n (%).
Abbreviations: UC, ulcerative colitis; CD, Crohn's disease; M, male; F, female; BMI, body mass index; CAI, clinical activity index; CDAI, clinical disease activity index.