SYSTEMATIC REVIEWS AND META-ANALYSES

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Efficacy and Safety of Medical Therapy for Low Bone Mineral Density in Patients With Inflammatory Bowel Disease: A Meta-analysis and Systematic Review

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The article has an accompanying continuing medical education activity on page e6. Learning Objectives—At the end of this activity, the successful learner will be able to establish the fact that bisphosphonates are effective and safe in the treatment of osteoporosis in inflammatory bowel disease patients.

BACKGROUND & AIMS: **Patients with inflammatory bowel disease (IBD) are at risk for osteoporosis and fracture. However, the efficacy of medical treatments for osteoporosis in increasing bone mineral density (BMD) in patients with IBD has not been well characterized.**

METHODS: **We conducted a meta-analysis and systematic review of controlled trials to evaluate the efficacy and safety of medical therapies used for low BMD in patients with IBD (Crohn's disease, ulcerative colitis, or indeterminate colitis). We searched MEDLINE, EMBASE, Google scholar, the University Hospital Medical Information Network (UMIN) Clinical Trials Registry, and Cochrane Central Register of Controlled Trials for studies that assessed the efficacy of medical treatment for low BMD in patients with IBD. We also manually searched abstracts from scientific meetings and bibliographies of identified articles for additional references. The primary outcome assessed was changes in BMD at the lumbar spine. We also collected data on hip BMD, numbers of new fractures, and adverse effects. Data were pooled by using random-effects models and by mixed-effects analysis for primary aims, when subgroup analysis by individual drug was possible.**

RESULTS: **We analyzed data from 19 randomized controlled studies; 2 used calcium and vitamin D as therapies, 13 used bisphosphonates, 4 used fluoride, 1 used calcitonin, and 1 used low-impact exercise. The pooled effect of bisphosphonates was greater than that of controls in increasing BMD at the lumbar spine (standard difference in means, 0.51; 95% confidence interval, 0.29–0.72) and hip (standard difference in means, 0.26; 95% confidence interval, 0.04–0.49) with comparable tolerability, and the risk of vertebral fractures was reduced. Fluoride increased lumbar spine BMD, but its ability to reduce risk of fracture was unclear. There was no evidence that the other interventions increased BMD.**

CONCLUSIONS: **On the basis of a meta-analysis, bisphosphonate is effective and well tolerated for the treatment of low BMD in patients with IBD and reduces the risk of vertebral fractures. There are insufficient data to support the efficacy of calcium and vitamin D, fluoride, calcitonin, or low-impact exercise. However, the small number of randomized controlled trials limited our meta-analysis.**

Keywords: CD; UC; Clinical Trial; Osteopenia; Estrogen.

Low bone mineral density (BMD) has a higher prevalence in patients with inflammatory bowel disease (IBD) as compared with the general population. This is considered to be due to the combination of the direct effect of systemic inflammation on bone, malabsorption of vitamin D, and increased glucocorticoid (GC) use.[1–3] BMD, which can be measured by dual-energy x-ray absorptiometry, is the single best predictor of fracture risk, and several studies have identified that fracture risk is increased in patients with IBD compared with the general population.[4,5] Patients with IBD typically develop disease at a young age and thereafter suffer

Abbreviations used in this paper: **BMD, bone mineral density; CD, Crohn's disease; CI, confidence interval; GC, glucocorticoid; IBD, inflammatory bowel disease; OR, odds ratio; SDm, standard difference in means; UC, ulcerative colitis.**

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from it during their lifetime. Effective and safe treatments for low BMD in IBD are needed to prevent complications such as fractures and disability.

The American Gastroenterological Association guidelines recommend dual-energy x-ray absorptiometry screening in IBD patients with the following risk factors: history of vertebral fractures, postmenopausal women, men >50 years of age, chronic GC therapy, or hypogonadism.[6] Pharmacologic interventions against osteoporosis include calcium and vitamin D supplementation, bisphosphonate, calcitonin, and hormone replacement therapies as well as treatment with fluoride and recombinant parathyroid hormone. Calcium and vitamin D supplementation is recommended to all IBD patients commencing GC therapy, and bisphosphonates are used in the setting of long-term GC use or in patients at high risk for fractures with a low t-score.[6,7] These recommendations have been mainly drawn from controlled studies in postmenopausal women and GC-treated patients for various inflammatory conditions; however, the mechanism of bone loss in IBD may be different. Up to 50% of patients with IBD have osteopenia, and approximately 15% are osteoporotic.[8] Low BMD has been associated with osteoporosis-related vertebral fractures.[8,9] The number of elderly IBD patients, who are more vulnerable to decreased BMD, are expected to increase over time, and effective measures to treat osteoporosis are required. IBD presents a unique challenge for drug therapy because it affects the gastrointestinal tract, which is the site of absorption for most drugs. This is further exacerbated by the fact that drugs such as bisphosphonates are poorly absorbed by the small bowel and are associated with esophageal and gastric mucosal irritation.[10,11]

Despite the high demand for effective and safe treatments for low BMD in IBD, there have been limited numbers of controlled trials regarding this problem, and most studies only included a small number of patients.[12–14] Thus, we decided to undertake this meta-analysis and systematic review to summarize and estimate the efficacy and safety of the available treatment options for low BMD in IBD patients.

Materials and Methods

Data Sources

We searched MEDLINE (1981–December 2011), EMBASE (1981–December 2011), Google scholar (1981–December 2011), UMIN Clinical Trials Registry (2005–December 2011), and Cochrane Central Register of Controlled Trials (Issue 4, October 2011) for studies assessing the efficacy of medical treatment for low BMD in patients with IBD. We also manually searched abstracts from scientific meetings (American College of Gastroenterology and American Gastroenterology Association, 2001–2011), and bibliographies of identified articles for additional references.

Search Strategy and Study Selection

To be eligible for inclusion, we only considered randomized controlled trials in patients with IBD (ie, Crohn's disease [CD], ulcerative colitis [UC], or indeterminate colitis) that compared outcomes between intervention and controlled arms. Controlled arms were placebo, no treatment, or another drug. There were no restrictions regarding age, sex, and duration of study. We imposed no geographic or language restrictions, and articles in languages other than English, Japanese, or German were translated where necessary. Two authors (J.M. and A.S.) independently screened each of the potential titles, abstracts, and/or full-texts to determine whether they were eligible for inclusion. Areas of disagreement or uncertainty were resolved by consensus between the 2 authors. The corresponding authors of studies were contacted to provide additional information on trials where required.

Studies were identified with the terms "Crohn disease", "Crohn's disease", "inflammatory bowel disease", "colitis", "ileitis", "regional enteritis", "ulcerative colitis", "IBD", "CD", or "UC" (both as medical subject headings and free text terms). These were combined by using the set operator and with studies identified with the terms "low bone density", "osteoporosis", "osteopenia" (both as medical subject headings terms and free text terms), or the following free text terms: "bisphosphonate", "calcium", "vitamin D", "estrogens", "raloxifen", "fluoride", "calcitonin", "alendronate", "etidronate", "ibandronate", "pamidronate", "risedronate", "tiludronate", "zoledronic acid", "exercise", "teriparatide", "denosumab", "parathyroid", and "hormone replacement". Search strategy is described in Figure 1.

Data Extraction and Quality Assessment

All data were independently abstracted in duplicate by 2 authors (J.M. and A.S.) by using a data abstraction form. Data on the study characteristics, such as author name, year of publication, country, sample size, mean age of patients, type of medication used, outcome, and incidence of adverse effects, were collected. The Jadad score, a scale that assesses the methodological quality of a clinical trial, was used to assess the quality of studies.[15]

Outcome Assessment

The primary outcome was improvement of BMD at the lumbar spine because this was the most commonly adopted primary outcome in studies evaluating the effect of medical intervention in treating or preventing low BMD. Secondary outcomes included improvement of BMD at the hip, incidence of fractures, adverse effects of therapy, and gastrointestinal side effects. Data were extracted as intention-to-treat analyses wherever trial reporting allowed this.