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ABOUT COVER

Editorial board of *World Journal of Gastroenterology*, Dr. Somashekar Krishna is an Associate Professor of Medicine in the Gastroenterology Division of the Ohio State University Wexner Medical Center in Columbus, OH, United States. He trained in advanced endoscopy at the University of Texas MD Anderson Cancer Center (Houston). Dr. Krishna has served on the American Society of Gastrointestinal Endoscopy Research Committee and the *Gastrointestinal Endoscopy* journal editorial board. He is a fellow of the ACG, AGA, and ASGE. Throughout his career, Dr. Krishna has published more than 125 peer-reviewed publications on his research, which encompass studies of advances in early and accurate detection of precancerous pancreatic lesions using novel endoscopic technologies, innovation in endoscopic ultrasound and novel imaging, endoscopy-guided ablation of pancreatic lesions, and large-database analyses and clinical outcomes with focus on acute pancreatitis. (L-Editor: Filipodia)

AIMS AND SCOPE

The primary aim of *World Journal of Gastroenterology* (*WJG*, *World J Gastroenterol*) is to provide scholars and readers from various fields of gastroenterology and hepatology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online. *WJG* mainly publishes articles reporting research results and findings obtained in the field of gastroenterology and hepatology and covering a wide range of topics including gastroenterology, hepatology, gastrointestinal endoscopy, gastrointestinal surgery, gastrointestinal oncology, and pediatric gastroenterology.

INDEXING/ABSTRACTING

The *WJG* is now indexed in Current Contents®/Clinical Medicine, Science Citation Index Expanded (also known as SciSearch®), Journal Citation Reports®, Index Medicus, MEDLINE, PubMed, PubMed Central, and Scopus. The 2020 edition of Journal Citation Report® cites the 2019 impact factor (IF) for *WJG* as 3.665; IF without journal self cites: 3.534; 5-year IF: 4.048; Ranking: 35 among 88 journals in gastroenterology and hepatology; and Quartile category: Q2.

RESPONSIBLE EDITORS FOR THIS ISSUE

SYSTEMATIC REVIEWS

Systematic review of the prevalence and development of osteoporosis or low bone mineral density and its risk factors in patients with inflammatory bowel disease

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Abstract

BACKGROUND

The inflammatory bowel diseases (IBD), Crohn's disease (CD) and ulcerative colitis (UC) are chronic, immune-mediated disorders of the digestive tract. IBD is considered to be a risk factor for developing osteoporosis; however current literature on this matter is inconsistent.

AIM

To assess prevalence and development of osteoporosis and low bone mineral density (BMD), and its risk factors, in IBD patients.

METHODS

Systematic review of population-based studies. Studies were identified by electronic (January 2018) and manual searches (May 2018). Databases searched included EMBASE and PubMed and abstracts from 2014-2018 presented at the United European Gastroenterology Week, the European Crohn's and Colitis Organisation congress, and Digestive Disease Week were screened. Studies were eligible for inclusion if they investigated either the prevalence of osteoporosis or osteopenia and/or risk factors for osteoporosis or low BMD in IBD patients. Studies on children under the age of 18 were excluded. Only population-based studies were included. All risk factors for osteoporosis and low BMD investigated in any included article were considered. Study quality and the possibility of bias were analysed using the Newcastle-Ottawa scale.

RESULTS

Twelve studies including 3661 IBD patients and 12789 healthy controls were included. Prevalence of osteoporosis varied between 4%-9% in studies including

both CD and UC patients; 2%-9% in studies including UC patients, and 7%-15% in studies including CD patients. Among healthy controls, prevalence of osteoporosis was 3% and 10% in two studies. CD diagnosis, lower body mass index (BMI), and lower body weight were risk factors associated with osteoporosis or low BMD. Findings regarding gender showed inconsistent results. CD patients had an increased risk for osteoporosis or low BMD over time, while UC patients did not. Increased age was associated with decreased BMD, and there was a positive association between weight and BMI and BMD over time. Great heterogeneity was found in the included studies in terms of study methodologies, definitions and the assessment of osteoporosis, and only a small number of population-based studies was available.

CONCLUSION
This systematic review found a possible increase of prevalence of osteoporosis in CD cohorts when compared to UC and cohorts including both disease types. Lower weight and lower BMI were predictors of osteoporosis or low BMD in IBD patients. The results varied considerably between studies.

Key Words: Inflammatory bowel disease; Osteoporosis; Systematic review; Epidemiology; Bone mineral density

Core Tip: Being diagnosed with inflammatory bowel disease (IBD) is considered a risk factor for development of osteoporosis, which leads to an increased risk of pathological fractures. This makes osteoporosis associated with great economic and psychological burden. Research made on the relationship between IBD and osteoporosis differs in study design and study populations, and results are inconsistent. The aims with this research are to assess the prevalence of osteoporosis among IBD patients compared to healthy individuals, assess the disease course of osteoporosis or low bone mineral density (BMD) in IBD patients and assess risk factors associated with osteoporosis and low BMD in IBD patients.

INTRODUCTION

The inflammatory bowel diseases (IBD), encompassing Crohn's disease (CD) and ulcerative colitis (UC) are chronic, immune-mediated disorders of the digestive tract of unknown aetiology. Being diagnosed with IBD is considered a risk factor for the development of osteoporosis, which leads to an increased risk of pathological fractures[1]. It is hypothesized that the severity and extent of gut inflammation and intestinal malabsorption leading to calcium and vitamin D deficiency in IBD patients might have a detrimental effect on bone[2-4]. Other known risk factors for osteoporosis, that also apply to the population without IBD are female gender, older age, low BMI and smoking[2-5]. As bone-protecting factors, physical activity has been found to have beneficial effects on both bone and cartilage in patients with osteoporosis, whether it's glucocorticoid-induced or not[6-8].

While osteoporosis is asymptomatic before fractures occur, the development of osteoporotic fractures as a consequence makes osteoporosis associated with great economic and psychological burden[9,10]. Several studies have investigated the relationship between inflammatory bowel diseases and osteoporosis but differences in study design and study populations, as well as inconsistent results and diverging interpretations of them, make it difficult to draw firm conclusions.

With this systematic review, we aimed to assess the prevalence of osteoporosis among IBD patients compared to healthy individuals, as well as the disease course of

osteoporosis or low BMD in IBD patients. We also aimed to assess risk factors associated with osteoporosis and low BMD in IBD patients with the intention to find more substantial evidence as to the cause of osteoporosis or low BMD in this patient group.

MATERIALS AND METHODS

Protocol and registration
This systematic review was conducted in accordance with the MOOSE (Meta-analyses Of Observational Studies in Epidemiology) guidelines. Prior to data extraction and analysis, a protocol was registered with PROSPERO (ID CRD42018084259) that has been updated regularly.

Sources
Studies were identified through electronic searches and by manually reviewing the reference lists of these studies, as well as relevant review articles. Electronic searches were conducted on January 30, 2018. Databases searched included EMBASE and PubMed. Searches were adjusted where needed for each database. Terms related to "inflammatory bowel disease", "osteoporosis", "osteopenia" and "study design" were used. The detailed search strategy is presented in Supplementary Table 1. Prior to title and abstract screening, duplicates and articles written in a language other than English were excluded. Titles and abstracts were screened independently by two of the review's authors (SK/BL). Disagreement was resolved by consensus. Potentially eligible studies were read in full by the same two authors (SK/BL). Disagreements that could not be resolved by consensus were discussed with a third author (JB) until an agreement was reached. Screening and study selection were made using the review management tool Covidence (www.covidence.org).

The search for unpublished articles occurred between May 14-16, 2018, where abstracts from 2014-2018 presented at the United European Gastroenterology Week, the European Crohn's and Colitis Organisation congress, and Digestive Disease Week were screened. Only the European Crohn's and Colitis Organisation congress had published abstracts from 2018. The screening was made by searching for the terms "osteoporosis", "osteopenia", "bone mineral density" and "inflammatory bowel disease".

Study selection, eligibility criteria and quality assessment
Studies were eligible for inclusion if they investigated either the prevalence of osteoporosis or osteopenia and/or risk factors for osteoporosis or low BMD in IBD patients. Studies on children under the age of 18 were excluded. Only population-based studies were included. All risk factors for osteoporosis and low BMD investigated in any included article were considered.

Quality assessment and risk of bias assessment were performed using the Newcastle-Ottawa scale (NOS), a scale developed for assessment of nonrandomized studies including cohort studies[11]. Stars were given to each article based on criteria in the categories of "selection", "comparability" and "outcome". A maximum of nine stars could be allocated to any one study.

Data extraction
From each included study the following information was extracted: (1) Author, year of publication, study period, number of patients included, country of study; (2) Prevalence of osteoporosis in patient groups and, if included in the study, healthy control groups; (3) T, Z and BMD (g/cm^2) scores in patient groups and, if included in the study, healthy control groups; (4) Prevalence of osteoporosis and T, Z and BMD (g/cm^2) scores in subgroups including gender, type of IBD, age (>/< 50 years), treatment (steroid/non-steroid), previous surgery, and Montreal disease classification; (5) Information regarding changes in rates of osteoporosis over a period of time; and (6) All clinical and socio-demographic risk factors that are investigated to be associated with osteoporosis or lowering of BMD in IBD patients.

Dual-energy X-ray absorptiometry (DXA) is performed on several bone areas and studies were therefore expected to present both overall measurements and/or information on each specific area. Examining risk factors for osteoporosis or low BMD in IBD patients, we considered it an association if at least one measured bone area showed significant association to an investigated risk factor, or if at least one measured

bone area showed significantly lower BMD than that same area in a comparison group. If a study only presented the proportion of patients with osteoporosis in each individual bone area, the overall prevalence was defined as that in the bone area in which most patients had osteoporosis. Prevalence of osteopenia was not considered.

If several studies analyzed the same cohort, prevalence estimates and risk factors were only registered once for each cohort. Authors were contacted for possible unpublished data. Studies analyzing CD and UC patients combined are referred to as "IBD studies", while studies analyzing CD or UC exclusively are described as "CD studies" or "UC studies", respectively.

RESULTS

Study characteristics
The search identified 449 records. After removing duplicates, non-English language studies and screening abstracts, 84 full-text articles were assessed for eligibility. A total of 12 papers were included in our study, one[12] of which was found *via* screening of references. An overview of the number of titles, abstracts and full-text articles that were excluded, with justification for their exclusion, can be found in the PRISMA flow diagram, Figure 1. No conference abstracts matched our criteria for inclusion. Authors either declined to provide data or did not respond to our queries in eight cases.

A detailed overview of the characteristics of each study is presented in Table 1. The 12 studies were based on a total of seven cohorts. All twelve studies contributed with unique information despite the fact that some included the same cohort. Information was only registered once for each cohort. Six studies investigated only CD patients[12-17], while the remainder investigated both CD and UC patients. No studies investigated only CD patients. Four studies included a healthy control group[12,15,17,18]. Five were follow up studies[3,12,18-20]. Two studies investigated only premenopausal women[21,22]. Two studies presented only the number of patients that had osteoporosis in each measured bone area but no overall number[13,17]. The total population across all studies was 3661 IBD patients, of which 1833 (50%) were women and 1828 (50%) men. A total of 1546 (42%) patients had UC and 2115 (58%) had CD. The control groups consisted of 12789 healthy individuals.

Quality assessment
Table 2 provides detailed quality assessments of the studies according to the NOS. All included studies were allocated stars for the representativeness of the exposed cohort – the average IBD patient – since they are all population based. Osteoporosis was either diagnosed by DXA scan or from ICD-10 codes and hence all studies received at least two stars with regards to selection. With regards to comparability, gender and age were identified to be the most relevant confounding variables. With reference to outcome, 2 years were set as long enough follow-up time for outcomes (osteoporosis or change in BMD) to occur. A maximum of 25% of patients could be lost to follow up in order to receive a star for adequacy of follow up of cohorts.

Prevalence of osteoporosis (diagnosis based on T- and Z-scores or ICD-10 codes)
The prevalence of osteoporosis in IBD patients ranged from 2%[18] to 15%[16]. In patients with UC, this range was 2%-9%[18,19], while it was 7%-15%[16,18,19] in CD patients. Two studies provided age- and sex matched controls and in these the prevalence of osteoporosis was 3%[18] and 10%[17], respectively.

Risk factors for low bone mineral density
Nine studies based on six study cohorts investigated risk factors for osteoporosis or low BMD of which four, based on two study cohorts, investigated both UC and CD patients[19-22] and of which five, based on four study cohorts, investigated only CD patients[12-15,17]. An overview of the most relevant risk factors associated with osteoporosis or low BMD can be found in Table 3, while a detailed list can be found in Supplementary Table 2. Overall, a CD diagnosis, lower body mass index (BMI) and lower body weight were associated with osteoporosis or low BMD. Female gender was found to be associated with lower BMD in a study of both CD and UC patients[20]. In CD cohorts, one study found males to have lower BMD than women[12], one study found no significance[13] and one study found female gender to be predictive for decreased BMD[17]. Use of corticosteroids in any form and with any duration was found to be associated with osteoporosis or low BMD only in studies investigating CD

Table 1 Study characteristics

Ref.	Publication year	Country of study	Type of study	DXA scan[1]	No. of patients	Average age of patients	Cohort	Control group	Follow-up	Comments
Andreassen *et al*[1]	1998	Denmark	Cross-sectional study inviting all IBD patients from a well-defined area	Yes	115	37 (16-75); median (range)	CD only	No	No	
Andreassen *et al*[2]	1999	Denmark	Cross-sectional case-control study inviting all IBD patients from a well-defined area	Yes	113	37 (16-75); median (range)	CD only	Yes; *n* = 113	No	Same cohort used as in Andreassen *et al*[14] (1998)
Bernstein *et al*[3]	2003[2]	United States	Cross-sectional data extracted from population-based Manitoba IBD research registry	Yes	70; UC: *n* = 12; CD: *n* = 58	33.0 (7.4); mean (SD)	UC and CD	No	No	Includes only premenopausal women
Bernstein *et al*[4]	2003[3]	United States	Cross-sectional data extracted from population-based Manitoba IBD research registry	Yes	66 (DXA results: *n* = 70); UC: *n* = 11; CD: *n* = 55	33.3 (18-44); mean (range)	UC and CD	No	No	Includes only premenopausal women. Same cohort used as in Bernstein (2002)
Haugeberg *et al*[5]	2001	Norway	Cross-sectional data from a population-based study. Case control study	Yes	55	38.5 (12.7); mean (SD)	CD only	Yes; *n* = 52	No	
Jahnsen *et al*[6]	1997	Norway	Cross-sectional case control study	Yes	60	36 (21-75); median (range)	CD only	Yes; *n* = 60	No	Includes a cohort of UC patients that is not population-based which was therefore not included
Jahnsen *et al*[7]	2004	Norway	Follow-up study	Yes	60	36 (21-75); median (range)	CD only	No	Yes	Includes a cohort of UC patients that is not population-based which was therefore not included
									2 yr	Same cohort used as in Jahnsen (1997)
Leslie *et al*[8]	2008	Canada	Follow-up study with cohort extracted from population-based Manitoba IBD research registry	Yes	101; UC: *n* = 45; CD: *n* = 56	46.9 (15.5); mean (SD)	UC and CD	No	Yes; 2.3 ± 0.3 yr	
Leslie *et al*[9]	2009	Canada	Follow-up study with cohort extracted from population-based Manitoba IBD research registry	Yes	101 UC: *n* = 45 CD: *n* = 56	47 (15); mean (SD)	UC and CD	No	Yes; 2.3 ± 0.3 yr	Same cohort used as in Leslie *et al*[19] (2008)
Schoon *et al*[10]	2000	The Netherlands	Cross-sectional cohort	Yes	119	42 (14); mean (SD)	CD only	No	No	
Targownik *et al*[11]	2012	Canada	Follow-up study with data extracted from population-based Manitoba IBD research registry	Yes	86; UC: *n* = 32; CD: *n* = 50; Unclass: *n* = 4	46.7 (14.9); mean (SD); 46 (35-57) median (IQR)	UC and CD	No	Yes; 4.3 ± 0.3 yr	Same cohort used as in Leslie *et al*[19] (2008)
Tsai *et al*[12]	2015	Taiwan	Follow-up case control study with data extracted from population-based registry	No	3141; UC: *n* = 1489; CD: *n* = 1652	46.7 (35.6-61.0); median (IQR)	UC and CD	Yes; *n* = 12564	Yes; 6.49 ± 3.09 yr	Diagnosis of osteoporosis based on ICD-10 codes

[1]BMD scores derived from DXA scan.

[2]published in May.

3published in November. CD: Crohn's disease; UC: Ulcerative colitis; IQR: interquartile range; Unclass.: unclassified; IBD: inflammatory bowel diseases.

Table 2 Quality assessment according to the Newcastle–Ottawa Scale

	Schoon *et al*[13] (2000)	Jahnsen *et al*[12] (1997)	Jahnsen *et al*[16] (2004)	Tsai *et al*[18] (2015)	Targownik *et al*[3] (2012)	Leslie *et al*[20] (2009)	Leslie *et al*[19] (2008)	Andreassen *et al*[14] (1998)	Andreassen *et al*[15] (1999)	Bernstein *et al*[21] (2003, May)	Bernstein *et al*[22] (2003, November)	Haugeberg *et al*[17] (2001)
Selection	**	***	**	****	**	**	**	**	***	**	**	***
Comparability		**		**					**			**
Outcome	*	*	**	**	***	**	**	*	*	*	*	*
Total number of stars allocated	3	6	4	7	5	4	4	3	6	3	3	6

exclusively. Age was associated with osteoporosis or low BMD in studies including only CD patients, where one study found increased age to be a risk factor[15], and one study found patients with reduced BMD to be significantly younger than the patient group without reduced BMD[17].

Risk factors for change in bone mineral density over time

Five studies based on three cohorts analysed risk factors for a change in BMD over a period of time[3,16,18-20]. Follow-up for the studies varied between 2 years[16] and 6.49 ± 3.09 years[18]. One study included only CD patients[16]. An overview of the most relevant risk factors for change in BMD can be found in Table 4, while a detailed list of all risk factors can be found in Supplementary Table 3. CD patients appeared to have an increased risk of developing lower BMD or osteoporosis over time, while UC patients had no such increased risk. Gender analyses showed contradicting results. An increase in age was found to be associated with a decrease in BMD, whereas an increase (or decrease) in weight and BMI was associated with an increase (or decrease) in BMD.

DISCUSSION

This systematic review summarises the prevalence and development of, and risk factors for, osteoporosis or low BMD among patients with IBD. Though not statistically proven to be significant, it seems that CD cohorts have a higher prevalence of osteoporosis as compared to the UC cohorts. We found an association between

Table 3 Overview of most relevant risk factors for low bone mineral density or osteoporosis

Risk factors for reduced BMD	CD	CD + UC	Comments
General risk factors			
Gender[5,6,9,10]	+/-	+	Female gender was found to be significantly correlated by Leslie *et al*[20] (2009) investigating both CD and UC patients. In CD studies, Haugeberg *et al*[5] found female gender to be a predictive factor for osteoporosis. Jahnsen *et al*[6] found men to have lower Z-scores than women, whereas Schoon *et al*[10] found no significant association.
Age[2,3,5,9]	+	+/-	Age was significantly associated in the CD studies. However, Haugeberg *et al*[5] found patients with reduced BMD to be significantly younger than those without reduced BMD.
Weight[2,3,5,9]	+, -[1]	+	Low weight was found to be a risk factor for low BMD in both CD + UC cohorts. In CD cohorts, Andreassen *et al*[15] (1999) found a significant positive correlation only in males. Haugeberg *et al*[17] found a positive correlation between weight and BMD for both genders.
BMI[2,5,6,9]	+/-	+	Leslie *et al*[20] (2009), the only study investigating BMI in CD + UC, found a positive correlation between BMI and BMD. Haugeberg *et al*[17] found a significant association for CD patients in a bivariate analysis, but not in a multiple linear regression analysis.
Steroid treatment[2,3,5,6,9]	+/-[2]	-	Multiple risk factors related to steroid usage were investigated. No correlation was found in CD + UC. However, most CD studies did find a correlation.
Height[3,5,9]	+/-	+/-	
Smoking[3,5,6]	-	-	
Vitamin D supplement[3-5]	-	-	
Calcium supplement[3-5]	-	-	
Serum 25(OH)D[1,5,8]	+/-	+/-	
Serum calcium[1,5,8]	-	-	
Serum parathyroid hormone[1,5,8]	+/-	+	
Disease-specific risk factors			
UC diagnosis[3,9]	Not relevant	-	
CD diagnosis[3,6,9]	Not relevant	+/-	
Disease location[1,3,5]	-	-	
Disease duration[2,3,5,6]	+[3],-	-	
Surgery[2,3,5,6]	+/-	-	

[1]Only in females.

[2]Only in males.

[3]Postmenopausal females. A plus sign means that a significant association was found and a minus sign means that no association was found. If studies found different results, both signs are present. CD: Crohn's disease; UC: Ulcerative colitis; BMI: Body mass index; BMD: Bone mineral density; +: Positive association; -: No association; +/-: Significant association and no association were found, depending on the study and/or statistical analysis carried out.

osteoporosis or low BMD and lower weight and lower BMI in both CD cohorts and cohorts including both CD and UC patients. Two out of four studies investigating gender found female gender to be associated with lower BMD. Age and steroid usage were found to be associated only among CD cohorts. In cohorts that analysed change in BMD over time, increased age was associated with a decrease in BMD and increased weight and BMI were associated with increased BMD. Furthermore, and unlike UC patients, CD patients had an increased risk of osteoporosis or low BMD over time.

Prevalence of osteoporosis

The prevalence of osteoporosis among IBD patients ranged from 2%[18] to 15%[16], with a range of 2%[18] to 9%[19] in UC patients and 7%[18,19] to 15%[16] in CD patients. The prevalence among healthy controls was investigated in two studies and was found to be 3%[18] and 10% respectively[17]. Since the data for osteoporosis prevalence in some studies were extracted from measurements of only one bone area, these numbers

Table 4 Overview of the most relevant risk factors for change in bone mineral density over time

Risk factors for change in BMD	CD	CD + UC	Comments
General risk factors			
Gender[8,9,11,12]	No data	+/-	No difference was found between genders in one study cohort[8,9,12], whilst another cohort[11] found a greater incidence of osteoporosis in women than in men.
Age[8,9,11,12]	No data	+/-	
Weight[9,11]	No data	+	
BMI[7,9,11]	+	+	
Steroid treatment[7-9,11]	-	+/-	
Smoking[7]	-	No data	
Serum 25-OH D[7,8,11]	+	+/-	
Disease-specific risk factors			
Diagnosis[9,11,12]	Not relevant	+[1], -	One[13] out of three studies found CD to be associated with an increased risk of osteoporosis. The others found no associations.
Disease location[7]	-	No data	
Disease activity[11]	No data	-	

[1]Only in Crohn's disease. CD: Crohn's disease; UC: Ulcerative colitis; +: Positive association; -: No association; +/-: Significant association and no association were found, depending on the study and/or statistical analysis carried out. A plus sign means that a significant association was found and a minus sign means that no association was found. If studies found different results, both signs are present. Follow-up time for the respective studies was as follows: Jahnsen *et al*[16]: 2 yr; Leslie *et al*[19]: 2.3 ± 0.3 yr; Leslie *et al*[20]: 2.3 ± 0.3 yr; Targownik *et al*[3]: 4.3 ± 0.3 yr; Tsai *et al*[18]: 6.49 ± 3.09 yr.

could be underestimations. The available data did not allow for a meaningful comparison of IBD patients and healthy controls.

When looking at osteoporosis prevalence worldwide in people without IBD, the numbers vary. Approximately 172400 people (around 3%) had osteoporosis in Denmark in 2017 according to the Danish Health Authority[23] and The International Osteoporosis Foundation relies on the estimate that over 200 million people worldwide (around 3%) suffer from it[9]. However, it has been estimated that the actual number of people aged 50 years or older with osteoporosis in Denmark, including undiagnosed inhabitants, is between 146481 and 518272, depending of the calculation method[23]. A nationwide register based Danish study showed that the estimated prevalence of osteoporosis was 40.8% in women and 17.7 % in men, all ≥ 50 years[24]. Due to the wide range of estimates for the prevalence of osteoporosis and the small number of papers included in our study, it is not possible for us to conclude whether its overall prevalence is higher among IBD patients.

General risk factors for osteoporosis and low BMD

The included studies investigated many different risk factors using a variety of methodologies, making it difficult to draw firm, generalized conclusions. We found lower BMI and lower body weight to be associated with lower BMD. Female gender was found to be associated in two out of four studies investigating this risk factor. These are well-documented risk factors for osteoporosis in the background population as well[5].

Surprisingly, use of prednisolone in any dose and duration was found to be associated with decreased BMD in cross-sectional analyses only in CD patients. Steroids are well-recognized bone-resorbing agents[25,26]. Our finding might be explained by the fact that we have considered all forms of prednisolone use with any duration and hence the bones of some patients included in the analyses might have not been exposed enough to prednisolone to be affected[27].

Older age is a well-known risk factor for osteoporosis[5]. Remarkably, age showed significant association with BMD in studies including CD patients only, and one study found the patient group with reduced BMD to be younger than the patients with normal BMD. These studies were small and one of them only included premenopausal women. Hence the analysed population might not be fully representative.
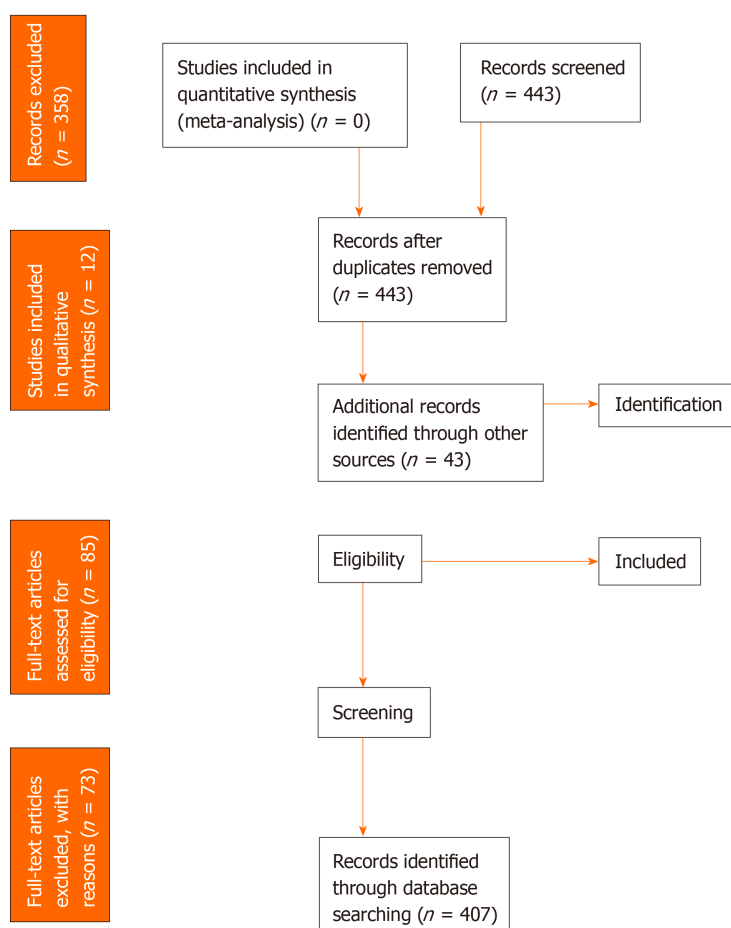
Figure 1 PRISMA flow diagram for the systematic review of the literature.

General risk factors for development of osteoporosis or low BMD over time

We found that increased age was associated with a decrease in BMD and that increased weight and BMI were associated with an increase in BMD over time. The results of analyses of gender and use of steroids showed no uniformity. These discrepant results are additionally surprising since females are known to be at higher risk of developing osteoporosis[5]. This might again be explained by the lack of large-scale studies and that one study only includes premenopausal women. The only register-based study included in our review concluded that female gender was a risk factor for osteoporosis[18].

Disease-specific risk factors

The CD cohorts presented the highest range in the prevalence of osteoporosis, though the numbers overlapped. CD, and not UC, appeared to be associated with osteoporosis or low BMD. Only CD patients seemed to have an increased risk for osteoporosis or low BMD over time. Suggested risk factors for developing osteoporosis are small-bowel disease or resection, smoking and corticosteroid treatment[28]. Small-bowel disease and resection are specific to CD and as such could partly explain why the risk of osteoporosis appears to be greater among CD patients. Moreover, CD patients have been shown to have a higher prevalence of smoking than UC patients[29]. Two population-based studies of CD and UC patients, respectively, have shown that on average around 2% of UC patients take corticosteroids at any given time, whereas almost 10% of CD patients do[30,31]. Future analyses ought to be made of UC and CD separately.

Gut inflammation is a disease-specific risk factor that few of the studies included here chose to analyse. According to a synopsis on research evaluating bone disease in patients with IBD from 2014, increased systemic inflammation increases bone resorption[1]. Inflammation serum markers and their role in IBD is an interesting subject that should be researched further.

Screening and treatment of osteoporosis

Current guidelines recommend that high risk IBD patients should be screened for osteoporosis[32,33]. A Danish study found in a cohort of 513 unselected IBD patients with ten years of follow-up that the incidence of osteoporosis was twice as high for IBD patients compared to a control population[34]. This indicates that adequate screening of osteoporosis could benefit IBD patients.

Strengths and limitations

There are several limitations to this systematic review. A systematic review is evidently dependent on the quality of the studies under review. The number of available studies was small, as was the number of patients in most cohorts. Furthermore, the quality of the studies reviewed varied considerably, as did the statistical analyses and use of covariates. This has precluded the possibility of performing a meta-analysis. Also, as all but one study originated in Europe, United States or Canada, their data might not be representative of other parts of the world. Half of the studies investigated only CD patients, while studies analysing both UC and CD patients did not provide stratified information on IBD subtype. Therefore, no data on UC patients exclusively were available. The risk factors discussed above were considered to be associated with osteoporosis if only one measurement (*e.g.*, total hip, femoral neck, *etc.*) was significant. Therefore, the association between BMD and some risk factors may vary in strength. The follow up time for the included studies varied between two and 6,5 years and hence may have been too short in some studies to identify any change in BMD. One study[18] excluded patients diagnosed with osteoporosis before their IBD diagnosis; to compare this study with other studies that did not exclude this patient group might have affected our results. Finally, analyses conducted during each study were based on different measurements, *i.e.*, T, Z, and BMD scores, and this may also have distorted our analyses.

CONCLUSION

In conclusion, there seems to be an increased prevalence of osteoporosis among CD, as compared to UC, patients. We found an association between osteoporosis or low BMD and lower weight and lower BMI for CD and UC patients while findings regarding gender were inconsistent across studies. Steroid usage was found to be associated with an increased risk of osteoporosis or low BMD only in patients with CD. Increase in age, decrease in weight and BMI, and diagnosis of CD seem to be associated with a decrease in BMD over time. Firm conclusions are difficult to draw due to considerable heterogeneity in terms of study methodologies, definitions and the assessment of osteoporosis, and the small number of population-based studies. Osteoporosis is a common disease that is associated with great economic and psychological burden worldwide due to the consequences of the disease in terms of osteoporotic fractures, and physicians treating patients with IBD should be aware of the risk for osteoporosis in this patient group. Given the importance of adequate screening and treatment of osteoporosis, there is a need for more prospective population-based research on the relationship between osteoporosis and IBD-patients and subgroups in this population. Any such future studies should assess CD and UC separately, should include healthy subjects as controls, and should assess disease specific risk factors such as gut inflammation markers.

ARTICLE HIGHLIGHTS

Research background

The inflammatory bowel diseases (IBD), encompassing Crohn's disease (CD) and ulcerative colitis (UC) are chronic, immune-mediated disorders of the digestive tract. Being diagnosed with IBD is considered a risk factor for the development of osteoporosis. The consequence of development of osteoporosis is the increased risk of pathological fractures that in turn are associated with great economic and psychological burden. Several studies have investigated the relationship between inflammatory bowel diseases and osteoporosis but differences in study design and study populations, as well as inconsistent results and diverging interpretations of them, make it difficult to draw firm conclusions.

Research motivation

Considering the severe consequences of osteoporosis, research on risk factors and prevalence of the disease in IBD patients is of great importance in order to conclude how prevailing the disease is in this patient group and its subgroups. It may give clues on how guidelines for screening and treatment of osteoporosis in IBD-patients should be developed, as well pinpointing what areas need more research.

Research objectives

The objectives with this research was to assess the prevalence of osteoporosis among IBD patients compared to healthy individuals, as well as the disease course of osteoporosis or low BMD in IBD patients. We also aimed to assess risk factors associated with osteoporosis and low BMD in IBD patients with the intention to find more substantial evidence as to the cause of osteoporosis or low BMD in this patient group.

Research methods

For this systematic review, we searched databases including EMBASE and PubMed as well as abstracts from 2014-2018 presented at the United European Gastroenterology Week, the European Crohn's and Colitis Organisation congress, and Digestive Disease Week were screened. Studies were eligible for inclusion if they investigated either the prevalence of osteoporosis or osteopenia and/or risk factors for osteoporosis or low bone mineral density (BMD in IBD patients. Studies on children under the age of 18 were excluded. Only population-based studies were included. All risk factors for osteoporosis and low BMD investigated in any included article were considered. Study quality and the possibility of bias were analysed using the Newcastle-Ottawa scale.

Research results

Twelve studies including 3661 IBD patients and 12789 healthy controls were included. Prevalence of osteoporosis varied between 4%-9% in studies including both CD and UC patients; 2%-9% in studies including UC patients, and 7%-15% in studies including CD patients. Among healthy controls, prevalence of osteoporosis was 3% and 10% in two studies. CD diagnosis, low body mass index (BMI) and low body weight were risk factors associated with osteoporosis or low BMD. Two out of four studies investigating gender found an association between female gender and lower BMD. CD patients had an increased risk for osteoporosis or low BMD over time, while UC patients did not. Increased age was associated with decreased BMD, and there was a positive association between weight and BMI and BMD over time. Great heterogeneity was found in the included studies in terms of study methodologies, definitions and the assessment of osteoporosis, and only a small number of population-based studies was available.

Research conclusions

This systematic review found a possible increase of prevalence of osteoporosis in CD cohorts when compared to UC and cohorts including both disease types. Lower weight and lower BMI were predictors of osteoporosis or low BMD in IBD patients. The results varied considerably between studies. Firm conclusions are difficult to draw due to considerable heterogeneity in terms of study methodologies, definitions and the assessment of osteoporosis, and the small number of population-based studies.

Research perspectives

Osteoporosis is a common disease that is associated with great economic and psychological burden worldwide due to the consequences of the disease in terms of osteoporotic fractures. Given the importance of adequate screening and treatment of osteoporosis, there is a need for more prospective population-based research on the relationship between osteoporosis and IBD-patients and subgroups in this population. Any such future studies should assess CD and UC separately, should include healthy subjects as controls, and should assess disease specific risk factors such as gut inflammation markers.

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