Alimentary Tract

Systematic review and meta-analysis of observational studies on the prevalence of fractures in coeliac disease

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Abstract

Background/Aims. Evidence of an increased bone fracture risk in coeliac disease is on debate. Our aim was to review systematically the current published information on fractures in coeliac disease and to perform a meta-analysis.

Methods. Case–control and cohort designs were identified by searching MEDLINE (1966–April 2007) and LILACS (1982–April 2007). Participants were adult coeliac disease patients of any sex and the outcome measure was the presence of any fracture. Studies were screened for inclusion by two authors who independently extracted the data. Methodological quality was assessed using the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology Statement) recommendations. Data were analysed using the RevMan Analyses statistical package in Review Manager (version 4.2.8) and reported as pooled odds ratio using a random effect model. Heterogeneity was investigated (standard χ^2 test) and sensitivity analysis was performed based on the reported quality and design type.

Results. While 60 of 405 studies met the initial screening criteria, only 8 met inclusion criteria after detailed review. These studies evaluated a total of 20,955 coeliac disease patients having 1819 (8.7%) fractures and 96,777 controls with 5955 (6.1%) fractures (pooled odds ratio = 1.43; 95% confidence interval 1.15–1.78) with considerable heterogeneity among studies ($p < 0.00001$).

Conclusions. Our meta-analysis confirms a significant association between bone fractures and coeliac disease. However, qualitative and quantitative differences among studies were evident. Further research is necessary to investigate the relevance of this heterogeneity.
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1. Introduction

Coeliac disease (CD) is common multisystemic, immune-mediated disorder induced by dietary proteins in wheat, rye and barley in genetically susceptible individuals. Although epidemiological studies have shown that the disease has an approximate prevalence of 0.3–1%, the majority of cases remain undiagnosed [1,2]. Despite the disease primarily affecting the gastrointestinal tract, its clinical presentation is highly variable with most patients having an indolent clinical course. While classical CD is dominated by gastrointestinal symptoms and malnutrition, atypical CD is characterised by few or no gastrointestinal complaints but extraintestinal manifestation predominant. Finally, family studies have facilitated the knowledge that a substantial proportion of patients may have no symptoms at all (silent CD). Recent large screening programs have noted a high prevalence of CD in the general population and that, up to two thirds of new patients are clinically silent cases [2]. Recognition of atypical features of CD is considered one of the responsible factors for the increased prevalence of the disorder, and now may be the most common clinical presentation [1].

Osteoporosis is a systemic skeletal disease characterised by a low bone mass and microarchitectural deterioration with a consequent increase in bone fragility and susceptibility to fracture [3]. Coeliac disease as a cause of bone mass and mineral metabolism deterioration and metabolic osteopathy was recognised in the scientific literature only some years ago [1–3]. Marked deformities, rickets and fractures were described as the prominent bone clinical features in the early

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literature. More recently, the advent of non-invasive techniques such as bone densitometry has demonstrated that an important number of CD patients are affected by impaired bone mass and have a potential risk of fractures [3]. Interestingly, bone mineral deterioration has been shown in patients with classical malabsorption symptoms but also in asymptomatic patients. Despite the strong body of information about bone metabolism in CD patients, its clinical relevance is far from being completely understood. Thus, the knowledge about the risk of fractures in CD patients has just been considered in recent years. The first study suggesting a high prevalence of fractures in CD patients compared with controls was published in 2000 [4]. While further authors confirmed such high prevalence of bone fracture, others failed to demonstrate such association. Therefore, reasonable doubts have been expressed about an increased risk of bone fracture [3].

Our aim in this study was to perform a systematic review and a meta-analysis of the current epidemiological information on the occurrence of fractures in CD patients.

2. Materials and methods

2.1. Criteria for considering studies for this review

The review was achieved following the Cochrane Collaboration steps [5] and the Meta-analysis of Observational Studies in Epidemiology (MOOSE) Group [6]. The types of studies considered to be included were controlled studies with case–control and cohort designs. Series of cases, descriptive reports and uncontrolled studies were excluded from the analysis. Participants in the studies were biopsy-proven CD patients of any sex with classical clinical presentation, atypical symptoms or silent clinical course. Papers with only paediatric population were excluded, while papers including children and adults were not discarded at first instance. The outcome measure was the proportion of patients with fractures.

2.2. Search strategy for identification of studies

Sources of published data included electronic databases (MEDLINE 1966–April 2007, LILACS – Latin American and Caribbean Centre on Health Sciences Information – 1980–April 2007) and there was no language restriction. Bibliographies of review articles were checked for additional studies not identified by the electronic search. The MEDLINE search strategy was as follows: "Osteoporosis" [MeSH] OR "Fractures, Bone" [MeSH] OR "Bone Diseases" [MeSH] OR "Bone Diseases, Metabolic" [MeSH] OR "Bone Density" [MeSH] AND "Celiac Disease" [MeSH].

2.3. Studies selection

The search results were screened independently by two qualified gastroenterologists (MO, MA) using titles of papers and abstracts. Once the relevant studies were identified, the full publication was retrieved and reviewed independently by the two investigators to determine suitability for final inclusion. Reviewers were not blind to the names of authors, institutions or journals. The two reviewers independently selected articles for inclusion according to pre-specified selection criteria and the inter-rater reliability was measured using kappa statistics. Disagreements were resolved by consensus, and when consensus could not be reached, by a third adjudicator (ES).

2.4. Quality assessments

Methodological quality was assessed independently by two reviewers (MO, MA) using the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology Statement) recommendations [7], with special consideration on selection bias, detection bias, performance bias and loss to follow-up. Three categories for quality assessment were established arbitrarily: A—when the study fulfilled more than 80% criteria stated in STROBE; B—when 50–80% of STROBE criteria were fulfilled; and C—if less than 50% criteria could be achieved. Inter-rater reliability was again assessed for quality scales by using kappa statistics and disagreement was resolved by consensus (HV, EM, JCB).

2.5. Data extraction and statistical analysis

Data on patients, methods, outcomes and results were extracted using a data extraction form (MO). Disagreement was resolved by other adjudicator (JCB). Data were analysed using the RevMan Analyses Version 1.0 for Windows (in Review Manager 4.2.8 Oxford, England): The Cochrane Collaboration 2002 [8]. Data were presented as relative risk (RR), odds ratio (OR) or hazard ratio (HR), along with their corresponding 95% confidence intervals (CI). Heterogeneity was investigated by using a standard χ^2 test with significance set at $p < 0.05$. Pooled OR and 95% CI were calculated using a random effect model. Sensitivity analysis was performed based on subgroups according to the reported quality and design type of the studies included. For qualitative assessment and the study selection criteria between reviewers, we used the decision analysis based on the kappa statistic (κ). The κ statistic uses the Cohen's Kappa method, where κ ranges from -1 to 1. A negative κ indicates absence of agreement. Kappa equal to 0 means no agreement among results beyond that expected by chance. Values >0.75 are considered to represent excellent agreement, whereas κ between 0.40 and 0.75 represents good agreement, and values <0.40 represent poor agreement.

3. Results

After the initial screening of 405 title and abstracts detected by the general search strategy, we identified 60
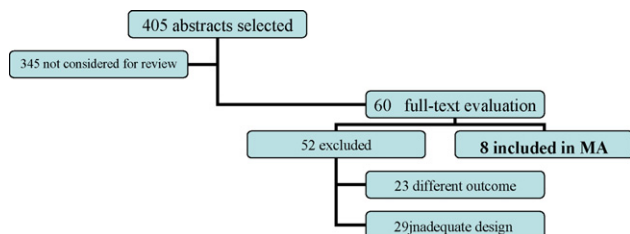
Fig. 1. Systematic review flow diagram.

papers (κ between reviewers = 0.85) that were evaluated in more detail. Of these, eight studies [4,9–15] (κ = 0.82) met the inclusion criteria for the meta-analysis (Fig. 1, flow chart). Main reasons for exclusion were a different outcome from bone fractures (*n*: 23) (in all of them the outcome measurement was the bone mineral density) and an inadequate design (*n*: 29).

The eight selected studies addressing the outcome of fractures in CD populations are outlined in Table 1. Overall, 20,955 CD patients have 1819 (8.7%) fractures and 96,777 controls with 5955 (6.15%) fractures (OR = 1.43; 95% CI 1.15–1.78) (Fig. 2). In addition, a considerable heterogeneity

among studies was determined. In this context, while six studies show a significant association between fractures and CD, two did not. Our evaluation evidenced a highly significant quantitative heterogeneity of studies (χ^2 47.06; $p < 0.00001$) as it was evidenced by the poor overlapping of confidence intervals for the individual studies.

As sensitivity analysis, we assessed study subgroups formed according to the quality of the results and the types of participants of each study. Firstly, we assessed studies excluding the one with the lowest precision based on a wide confidence interval. Thus, a highly significant heterogeneity still persists (χ^2 39.95; $p < 0.00001$) with a pooled OR indicative of an almost 50% increased risk of fractures for CD patients (OR = 1.27, 95% CI 1.20–1.34) (Fig. 3). Secondly, we analysed a subgroup involving studies only enrolling hospital-based participants (*n* = 4) (Fig. 4). In this assessment the heterogeneity was still highly significant (χ^2 16.08; $p < 0.001$) as was the risk of fractures in CD patients (OR = 1.70; 95% CI 1.40–2.07). Finally, our analysis of cohort studies reporting population-based data (*n* = 3) also exhibited heterogeneity (χ^2 14.55; $p = 0.0007$) and still a significantly increased prevalence of fractures in CD patients (OR = 1.23, 95% CI 1.16–1.31) (Fig. 5).
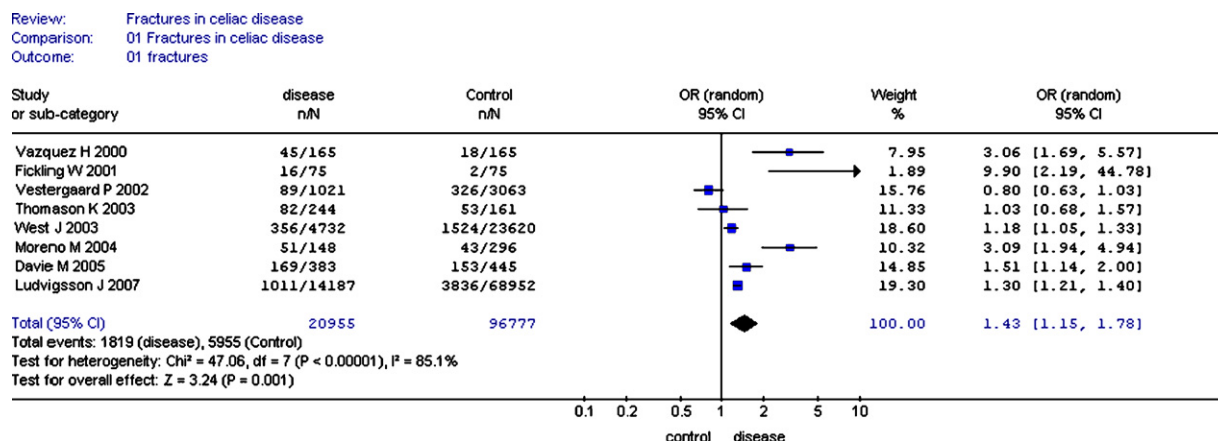

Fig. 2. Meta-analysis: overall, 1819 (8.7%) events (fractures) were detected in 20,955 CD patients, and 5955 (6.15%) in 96,777 controls (pooled OR = 1.43; 95% CI 1.15–1.78).
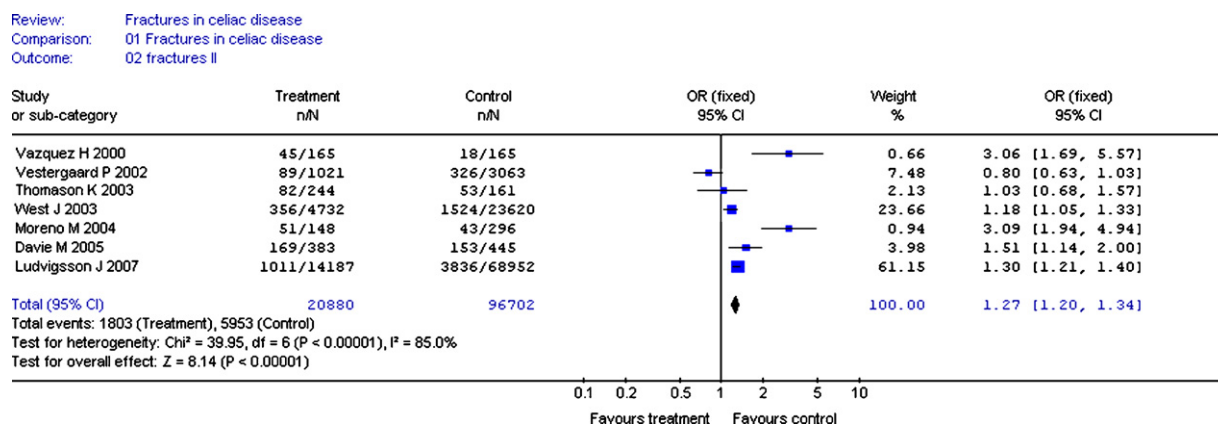

Fig. 3. Meta-analysis excluding the study with the least weight (pooled OR = 1.27, 95% CI 1.20–1.34).
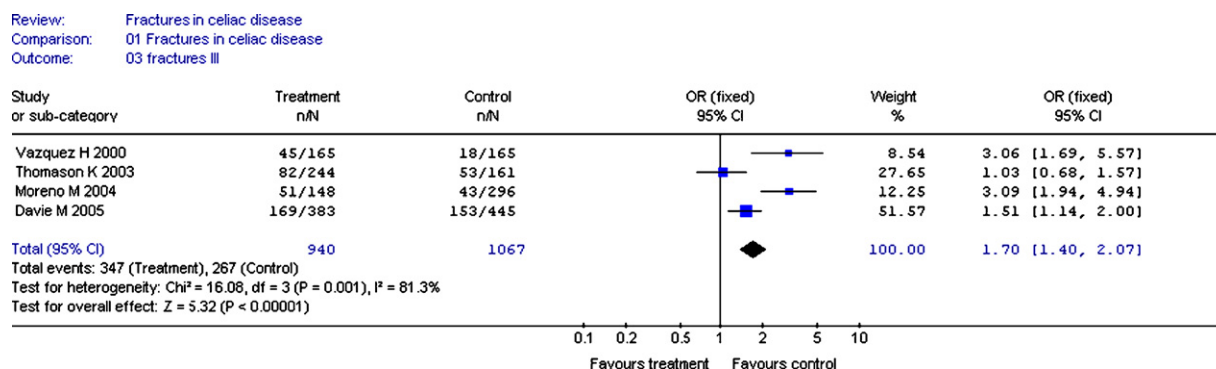
Fig. 4. Meta-analysis with studies enrolling hospital-based participants ($n = 4$) (pooled OR = 1.70; 95% CI 1.40–2.07).

3.1. Description of studies (Table 1)

The first controlled study addressing the fracture risk in CD patients was published by our group in Argentina and enrolled subjects from a malabsorption clinic [4]. In this retrospective case–control study based on data obtained from personal interviews performed by expert physicians and reports in files, we found that 25% (45 of 165) of CD patients had 1–5 fractures compared with 8% of age- and sex-matched controls. While all fractures were significantly increased in patients, 80% of them occurred in the peripheral skeleton and the spinal skeleton was not significantly affected. Furthermore, the most common site of fractures was the wrist and the majority of them occurred prior to diagnosis of CD. Although the mean time from the beginning of symptoms to CD diagnosis was longer in patients with fractures, this fact did not reach statistical significance.

Shortly after the first publication, Fickling et al. [9] reported another case–control study in CD patients attending a GI outpatients department and found a higher prevalence of a prior history of fractures in patients. The reported prevalence of fractures in patients and controls was based on data obtained from self-administered questionnaires. Thus, the risk of fracture before the diagnosis of CD was significantly higher than in controls, while was not different after the institution of a gluten-free diet. Interestingly, although the statistical analysis evidenced significant results, the 95% CI was particularly wide in both periods (OR = 5.62; 95% CI 1.09–38.62 and OR = 3.17; 95% CI 0.55–23.10, respectively) suggesting less precise results than in other studies.

In a population-based study from Denmark, Vestergaard and Mosekilde [10] reported the prevalence of fractures evaluated in individuals with CD captured from hospital discharge data. Compared with controls, the authors did not find increase rate of fractures in CD patients (RR = 0.94; 95% CI 0.71–1.24) both before (RR = 0.70; 95% CI 0.45–1.09) and after diagnosis of CD (RR = 0.90; 95% CI 0.72–1.12).

In a case–control study, Thomason et al. [11] used self-reported data from 244 patients with biopsy-proven CD attending a secondary care institution. The authors found that bone fractures were not significantly increased with respect to controls (OR = 1.05; 95% CI 0.68–1.02), although there was a trend to increased wrist fractures (OR = 1.21; 95% CI 0.66–2.25). In addition, the authors did not find any association between fractures and CD either before or after diagnosis of CD.

West et al. [12] in the largest population-based study from a United Kingdom primary care database found an increased fracture rate compared with controls. They demonstrated significant hazard ratios of 1.3 (95% CI 1.16–1.46) and 1.9 (95% CI 1.2–3.02) for all type of fracture and hip fracture, respectively. The authors did not find a difference in fracture risk comparing the prevalence assessed before and after diagnosis of CD (HR = 1.07; 95% CI 0.77–1.50). Moreover, incident and prevalent CD cases did not have differences in the risk of fractures.
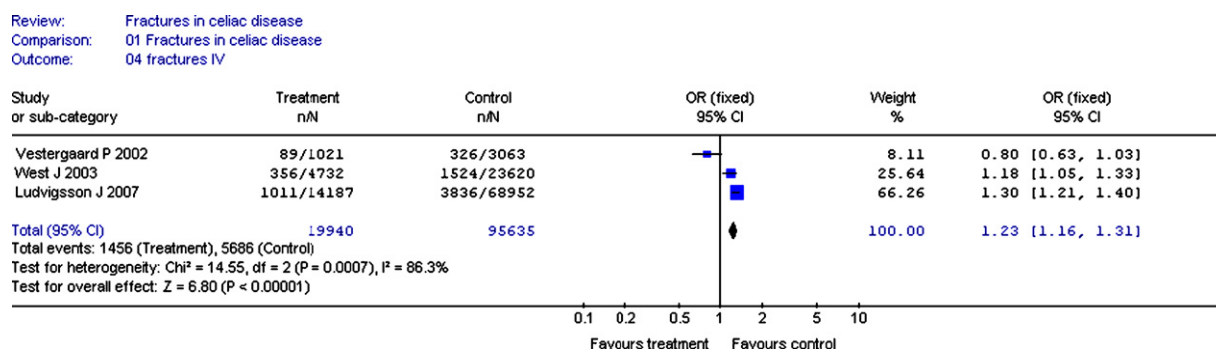

Fig. 5. Meta-analysis with only cohort studies reporting population-based data ($n = 3$) (pooled OR = 1.23, 95% CI 1.16–1.31).

Table 1
Summary of characteristics of studies included in the systematic review

Author, publication year, country	Design	Participants	Outcomes effect size 95% CI	Quality assessment
Vazquez et al., 2000 [4]	Case–control, interview	165 CD (143 F, 22 M; mean age 40 years) from the Malabsorption Clinic 165 controls (143 F, 22 M; mean age 41 years)	All fractures (45/165 in CD; 18/165 in controls) OR = 3.5 (1.8–7.2) Spine deformities OR = 2.8 (0.7–11.5)	B
Fickling et al., 2001, UK [9]	Case–control, questionnaire-based	75 CD (60 F, 15 M; mean age 52 years) recruited from the GI outpatient department 75 controls (60 F, 15 M; mean age 52 years)	All fractures (16/75 in CD; 2/75 in controls) OR = 9.90 (2.05–65.04) Before diagnosis ($n = 10$) OR = 5.62 (1.09–38.62) After diagnosis ($n = 6$) OR = 3.17 (0.55–23.61)	C
Vestergaard and Mosekilde, 2002 [10]	Retrospective cohort, databases (16 years)	1021 CD (588 F, 433 M; mean age 31 years) 3063 controls (1764 F, 1299 M; mean age 31 years)	All fractures (89/1021 in CD; 326/3063 in controls) RR = 0.94; 95% CI 0.71–1.24 Before diagnosis RR = 0.70 (95% CI 0.45–1.09) After diagnosis RR = 0.90 (0.72–1.12)	A
Thomason et al., 2003, UK [11]	Case–control, questionnaire	244 CD (171 F, 73 M; mean age 60 years) 161 controls (115 F, 46 M; mean age 61 years)	All fractures (82/244 in CD; 53/161 in controls) OR = 1.05 (0.68–1.62)	B
West et al., 2003, UK [12]	Retrospective cohort, databases (15 years)	4732 CD (3095 F, 1637 M; mean age 43.5 years) 23,620 controls (18,545 F, 5075 M; mean age 43.5 years)	All fractures (356/4732 in CD; 1524/23,620 in controls) HR = 1.30 (1.16–1.46) Hip fractures HR = 1.90 (1.20–3.02) Ulna/radius HR = 1.77 (1.35–2.34)	A
Moreno et al., 2004 [13]	Case–control, questionnaire and interview	148 CD (117 F, 31 M; mean age 41 years) 296 controls (236 F, 60 M; mean age 41 years)	All fractures (51/148 in CD; 43/296 in controls) OR = 3.6 (1.7–7.5) Symptomatic CD OR = 5.2 (2.8–9.8); subclinical CD OR = 1.7 (0.7–4.4)	B
Davie et al., 2005, UK [14]	Case–control, questionnaire-based	383 F CD (mean age 61 years) 445 F controls (mean age 61 years) Only women, recruited from GI and clinical units.	All fractures (169/383 in CD; 153/445 in controls) OR = 1.51 (1.13–2.02) Fractures after 50 years OR = 2.20 (1.49–3.25) More than 1 fracture OR = 2.96 (1.81–4.83)	B
Ludvigsson et al., 2007, Sweden [15]	Retrospective cohort, databases (39 years)	14,187 CD (8311 F, 5876 M; mean age 53 years) 68,952 controls (40,430 F, 28,522 M; mean age 53 years)	All fractures (1011/14,187 in CD; 3836/68,952 in controls) HR = 1.40 (1.3–1.5) Hip fractures HR = 2.1 (1.8–2.4)	A

CD: coeliac disease; F: female, M: male; OR: odd ratio; 95% CI: 95% confidence interval; HR: hazard ratio; RR: relative risk; *n*: number of patients. Quality assessment was performed by two authors (MO and MA) according to STROBE recommendations (see Section 2).

Recently, Moreno et al. [13] compared fracture rates detected in 148 CD patients (53% with a classically symptomatic disease at diagnosis, 36% with atypical CD and 11% of silent cases detected by screening) with that assessed in 296 age- and sex-matched controls with functional GI disorders. The study population was different to that previously reported by the same group [4] but data recollection was done using a similar protocol. The study determined an overall increased

risk of fractures in CD patients (OR = 3.6; 95% CI 1.7–7.5). Furthermore, the analysis evidenced a significantly increased number of peripheral fractures for classically symptomatic subjects compared with controls (OR = 5.2; 95% CI 2.8–9.8), but not in subjects with atypical/silent CD.

More recently, Davie et al. [14] reported a case–control study based on a self-reported questionnaire collecting historical data from female CD patients over 50 years old. Compared with age-matched non-CD controls, patients had a significantly higher number of bone fractures (OR = 1.51; 95% CI 1.13–2.02). Interestingly, this association was greater for events occurring after 50 years of age (OR = 2.20; 95% CI 1.49–3.25). No excess of fracture risk was found more than 10 years before diagnosis but the increased risk was evident in the period lapsed between 10 years before diagnosis and 5 years after diagnosis.

Finally, Ludvigsson et al. [15] reported the most recent analysis involving the largest population-based cohort study published so far. The authors demonstrated an increased risk in patients with CD for hip fracture (HR = 2.1; 95% CI 1.8–2.4) and for fractures of any type (HR = 1.4; 95% CI 1.3–1.5). The risk of complications may be greatest in the immediate years prior to or after a diagnosis of CD, but less so in the distant past or after many years with the gluten-free diet.

4. Discussion

There is a general consensus on that CD predisposes to metabolic osteopathy [1–3]. Thus, our systematic review identified a great number of papers (>400) recognising the association between CD and bone metabolic alterations. This body of evidence strongly suggests that CD should be considered as one of the leading conditions predisposing to bone damage. However, although bone derangement in CD was first reported several years ago, the true clinical magnitude of the problem was ignored for a long time and epidemiological information on fractures has only recently been acquired [4]. Moreover, the evidence of any association is controversial and only few studies addressed fractures as the outcome of interest [4,9–15]. This uncertainty deserves to be clarified in order to drive more realistic and objective diagnostic and therapeutic decisions on patient management. Thus, we performed a systematic review and meta-analysis of the available literature to evaluate the association of bone fractures with CD. Our search of related studies was exhaustively performed including retrieval from MEDLINE and LILACS avoiding language bias and it was complemented by manual checking in narrative review references. A publication bias associated with the tendency of reporting results in only one direction was considered unlikely since positive and negative results with respect to the association between CD and fractures were found.

Our present systematic review and meta-analysis evidence a significantly increased association between fractures and CD. Overall, the increased risk of fractures determined in the meta-analysis is 43% greater in CD patients compared with control subjects. However, a significant quantitative heterogeneity among studies was detected with six papers [4,9,12–15] showing an increased prevalence of fractures but two others [10,11] not evidencing significant differences with the control population. This quantitative heterogeneity was clearly shown in Fig. 2 where the statistical analysis determined a χ^2 value of 47.06 ($p < 0.00001$). Furthermore, our detailed analysis of each study also suggests qualitative differences among them. The heterogeneity of results in this study may be due to several reasons. Thus, the diversity among study populations, a lack of clinical characterization of patients in some studies and varied form of collection of clinical data (through personal interviews, self-administered questionnaires, records, discharge registers, general practice database, etc.) seem to be the most relevant factors leading to the evident heterogeneity. By analogy with studies dealing with the prevalence of osteopenia/osteoporosis in CD, studies addressing the prevalence of bone fractures should also consider with caution potential confounding factors such as, differences in terms of age of the studied population, duration of the disease, diagnostic delay, etc.

Due to the quantitative and qualitative heterogeneities evidenced, we further performed a sensitivity analysis based on two different criteria. Firstly, we excluded the study supporting a positive association but presenting the poorest statistical precision (with the widest 95% CI) [9]. Thus, taking in consideration seven studies (five showing a positive association and two reporting a negative one) a 27% increased risk of fractures was evident (Fig. 3). However, a highly significant heterogeneity remained despite exclusion of the study. Secondly, in an additional sensitivity analysis, we segregated studies according to the type of participants. Thus, two different subgroups were evident, studies enrolling patients attending specialised hospital units (four studies) (Fig. 4) [4,11,13,14], and those reporting population-based data (three studies) (Fig. 5) [10,12,15]. Interestingly, both strategies have demonstrated a significant higher prevalence of bone fractures.

Inevitably, studies brought together into a systematic review will differ qualitative and quantitatively. Thus, variability in the considered participants is assumed as clinical diversity, and variability in the investigation design and quality is referred as methodological diversity. The significant statistical heterogeneity arising from methodological diversity suggests that the studies are not all estimating the same quantity, but does not necessarily suggest that the true effect varies. In particular, heterogeneity associated solely with methodological diversity would indicate that the studies suffer from different degrees of bias. Some argue that since clinical and methodological diversity always occur in a meta-analysis, statistical heterogeneity is inevitable. Thus, the test for heterogeneity is irrelevant to the choice of analysis; heterogeneity in epidemiological studies will always exist whether we will be able to detect it using a statistical test or not [5].

A factor limiting the strength of the evidence presented in our systematic review is the fact that the studies included had differences in design. Additional factors limiting our observations include differences among studies in the selection of cases and controls, inadequate sample size, method used to ascertain fractures, and failure to precise duration of CD. In this context, we believe that the clinical characterization of participants should be relevant to the qualitative heterogeneity as it is suggested in the study of Moreno et al. [13] where the risk of fracture was increased in patients with classical CD but did not differ significantly from controls in atypical and silent cases. This observation is in concordance with most reports on densitometry in CD where there is a general agreement on that adult patients with classical symptoms suffer a more severe bone affectation [16–24].

In conclusion, the present systematic review and meta-analysis confirms a significant association between bone fractures and CD. However, although this assumption is confirmed by sensitivity analyses, qualitative and quantitative differences among studies were evident. Further research is necessary to investigate the relevance of this heterogeneity and to determine additional factors involved in the CD-associated fracture risk. We think that the identification of a subgroup of patients with an increased risk of fractures is very important in order to concentrate diagnostic and therapeutic strategies to provide a cost-effective healthcare of patients.

> ## Practice points
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> - The systematic review and meta-analysis confirm a positive association between bone fractures and coeliac disease in adult patients.
> - There are significant qualitative and quantitative heterogeneities among studies.
> - Although the effect was shown by both, studies based on patients attending specialised hospital units and those reporting population-based data, it seems evident that the risk of fractures is not similar in all patients.

> ## Research agenda
>
> - Further research is necessary in order to clarify, at least, two scanty known topics: (a) the identification of predictors of the increased risk of fractures and (b) exploring the potential protective effect of the gluten-free diet.

References

[1] National Institutes of Health Consensus Development Conference Statement on Celiac Disease, June 28–30, 2004. Gastroenterology 2005;128:1–9.

[2] Jones RB, Robins GG, Howdle P. Advances in celiac disease. Curr Opin Gastroenterol 2006;22:117–23.

[3] Corazza GR, Di Stefano M, Mauriño E, Bai JC. Bones in coeliac disease: diagnosis and treatment. Best Pract Res Clin Gastroenterol 2005;19:453–65.

[4] Vasquez H, Mazure R, Gonzalez D, Flores D, Pedreira S, Niveloni S, et al. Risk of fractures in celiac disease patients: a cross-sectional, case-control study. Am J Gastroenterol 2000;95:183–9.

[5] Higgins JPT, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions 4.2.5 (updated May 2005). In: The Cochrane Library, issue 3. Chichester, UK: John Wiley & Sons, Ltd.; 2005.

[6] Stroop D, Berlin J, Morton S, Olkin I, Williamson GD, Rennie D, et al., for the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) Group. Meta-analysis of observational studies in epidemiology. J Am Med Assoc 2000;283:2008–12.

[7] http://www.strobe-statement.org/PDF/STROBE-Checklist-Version3.pdf.

[8] RevMan Analyses Version 1.0 for Windows, in Review Manager 4.2. Oxford England: The Cochrane Collaboration 2002.

[9] Fickling WE, McFarlane XA, Bhalla AK, Robertson DA. The clinical impact of metabolic bone disease in coeliac disease. Postgrad Med J 2001;77:33–6.

[10] Vestergaard P, Mosekilde L. Fracture risk in patients with celiac Disease, Crohn's disease, and ulcerative colitis: a nationwide follow-up study of 16,416 patients in Denmark. Am J Epidemiol 2002;156:1–10.

[11] Thomason K, West J, Logan RF, Coupland C, Holmes GK. Fracture experience of patients with coeliac disease: a population based survey. Gut 2003;52:518–22.

[12] West J, Logan RF, Card TR, Smith C, Hubbard R. Fracture risk in people with celiac disease: a population-based cohort study. Gastroenterology 2003;125:429–36.

[13] Moreno ML, Vazquez H, Mazure R, Smecuol E, Niveloni S, Pedreira S, et al. Stratification of bone fracture risk in patients with celiac disease. Clin Gastroenterol Hepatol 2004;2:127–34.

[14] Davie MW, Gaywood I, George E, Jones PW, Masud T, Price T, et al. Excess non-spine fractures in women over 50 years with celiac disease: a cross-sectional, questionnaire-based study. Osteoporos Int 2005;16:1150–5.

[15] Ludvigsson JF, Michaelsson K, Ekbom A, Montgomery SM. Coeliac disease and the risk of fractures—a general population-based cohort study. Aliment Pharmacol Ther 2007;25:273–85.

[16] Kemppainen T, Kroger H, Janatuinen E, Arnala I, Kosma VM, Pikkarainen P, et al. Osteoporosis in adult patients with celiac disease. Bone 1999;24:249–55.

[17] Pistorius LR, Sweidan WH, Purdie DW, Steel SA, Howey S, Bennett JR, et al. Coeliac disease and bone mineral density in adult female patients. Gut 1995;37:639–42.

[18] Corazza GR, Di Sario A, Cecchetti L, Tarozzi C, Corrao G, Bernardi M, et al. Bone mass and metabolism in patients with celiac disease. Gastroenterology 1995;109:122–8.

[19] Gonzalez D, Mazure R, Mautalen C, Vazquez H, Bai J. Body composition and bone mineral density in untreated and treated patients with celiac disease. Bone 1995;16:231–4.

[20] Armagan O, Uz T, Tascioglu F, Colak O, Oner C, Akgun Y. Serological screening for celiac disease in premenopausal women with idiopathic osteoporosis. Clin Rheumatol 2005;24:239–43.

[21] Sanders DS, Patel D, Khan FB, Westbrook RH, Webber CV, Milford-Ward A, et al. Case-finding for adult celiac disease in patients with reduced bone mineral density. Dig Dis Sci 2005;50: 587–92.

[22] Stenson WF, Newberry R, Lorenz R, Baldus C, Civitelli R. Increased prevalence of celiac disease and need for routine screening among patients with osteoporosis. Arch Intern Med 2005;165:393–9.

[23] O'Leary C, Feighery C, Feighery A, Quane K, Shanahan F, Molloy M, et al. The prevalence of coeliac disease among female subjects having bone densitometry. Ir J Med Sci 2002;171:145–7.

[24] Drummond FJ, Annis P, O'Sullivan K, Wynne F, Daly M, Shanahan F, et al. Screening for asymptomatic celiac disease among patients referred for bone densitometry measurement. Bone 2003;33:970–4.