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Systematic review with meta-analysis: the prevalence of coeliac disease in patients with osteoporosis

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Summary

Background: Earlier studies have produced highly varying risk estimates for the prevalence of coeliac disease (CD) in osteoporosis.

Aims: To investigate the prevalence of CD among individuals with osteoporosis.

Methods: We conducted a systematic review of articles published in PubMed, Medline or EMBASE through May 2017 to identify studies looking at prevalence of CD in patients with osteoporosis. Search terms included "coeliac disease" combined with "fractures", "bone disease", "bone density", "densitometry", "osteoporos*", "osteomal*", "osteodys" or "dexa" or "dxa" or "skelet". Non-English papers with English-language abstracts were included. We used fixed-effects inverse variance-weighted models, and tested heterogeneity through subgroup analysis as well as through meta-regression.

Results: We identified eight relevant studies, comprising data from 3188 individuals with osteoporosis. Of these, 59 individuals (1.9%) had CD. A weighted pooled analysis demonstrated biopsy-confirmed CD in 1.6% (95% CI = 1.1%-2.0%) of individuals with osteoporosis. The heterogeneity was moderate (I^2 = 40.1%), and influenced by the underlying CD prevalence in the general population. After adding four studies (n = 814) with CD defined as positive tissue transglutaminase or endomysial antibodies, the pooled prevalence was comparable (1.6%; 95% CI = 1.2%-2.0%).

Conclusions: About 1 in 62 individuals with osteoporosis, or 1.6%, have biopsy-verified CD. This prevalence is comparable to that in the general population. These findings argue against routinely screening patients with osteoporosis for CD, which is contrary to current guideline recommendations. Additional studies are needed to determine the true utility of such screening programs.

Monika Laszkowska and Srihari Mahadev contributed equally.

As part of AP&T's peer-review process, a technical check of this meta-analysis was performed by Dr Y Yuan. The Handling Editor for this article was Professor Peter Gibson, and it was accepted for publication after full peer-review.

1 | INTRODUCTION

Coeliac disease (CD) is a life-long immune-mediated disease that is triggered by exposure to gluten in genetically sensitive individuals.[1] It is characterised by small intestinal inflammation and villous atrophy (VA) in the small intestine.[2] Individuals with CD are at increased risk of a number of complications including other gastrointestinal diseases,[3,4] as well as extraintestinal disease, malignancy[5] and death.[6]

Small intestinal VA leads to malabsorption of nutrients, and CD patients may present with not only weight loss and diarrhoea, but also fractures. A recent meta-analysis reported that CD patients are at a 30% increased risk of any fracture and at a 69% increased risk of hip fracture.[7] Furthermore, another recent meta-analysis found that patients with CD had an increased risk of osteoporosis (OR 2.73, CI 1.86-3.99),[8] as did one large screening study.[9] These studies did not, however, examine the risk of CD in patients first diagnosed with osteoporosis. Such information is crucial for clinicians as this will guide whether they should screen individuals with osteoporosis for CD. The reported prevalence of CD in individuals with osteoporosis has varied between 0%[10] and 33%.[11] While these two studies[10,11] represent extremes, there is also variability among the two largest studies so far,[12,13] where the CD prevalence in individuals with osteoporosis varied between 1.1% and 1.9%.

The primary aim of this systematic review was to examine the prevalence of CD in individuals with osteoporosis. A secondary aim was to investigate if the prevalence of CD varies between subgroups of individuals with osteoporosis.

2 | METHODS

For this paper we followed the PRISMA guidelines.[14]

2.1 | Search

The Karolinska Institutet Library searched PubMed and EMBASE for coeliac disease (or celiac disease) combined with "fractures", "bone disease", "bone density", "densitometry", "osteoporos*", "osteomal*", "osteodys" or "dexa" or "skelet" or "dxa" up until May 2017. We restricted our search to English-language abstracts. The review of all search results was conducted by ML and SM. Eight studies were deemed as relevant for our study (Table 1[12,13,15-20]; Figure S1 includes a flowchart for study inclusion).

2.2 | Inclusion and exclusion criteria

This meta-analysis included all studies that looked at the prevalence of biopsy-proven CD in patients with osteoporosis, based on the WHO definition. We excluded studies if they did not specify how osteoporosis was diagnosed, included patients with osteopenia or possible osteopenia, did not confirm CD diagnosis on biopsy, had a high risk of selection bias, did not clarify the absolute numbers of coeliac patients found in the population, or studies for which full text articles were not available. Table S1 reviews the definition of osteoporosis used for this meta-analysis.

TABLE 1 Papers included in the systematic review on coeliac disease prevalence in osteoporosis

Study (year)	Country	Percent	Coeliac patients, N	Osteoporosis patients, N
Nuti (2001)[16]	Italy	2.4	6	255
O'Leary (2002)[17]	Ireland	2.1	3	140
Sanders (2005)[18]	United Kingdom	2.1	5	243
Stenson (2005)[19]	United States	3.4	9	266
Legroux-Gerot (2009)[20]	France	0	0	140
Fojtik (2011)[12]	Czech Republic	1.9	30	1584
Gusso (2014)[15]	Brazil	1	1	100
Shahbazkhani (2015)[13]	Iran	1.1	5	460

All included studies can be regarded as prevalence studies since for the few case–control studies we only used information from the individuals with osteoporosis.

2.3 | Coeliac disease

We required a small intestinal biopsy for diagnosis (while we did not require a positive serology for diagnosis, the vast majority of patients were positive for relevant antibodies). A number of studies reporting that they confirmed the CD diagnosis through small intestinal biopsy did not clarify if Marsh II or Marsh III histopathology was required for diagnosis. In these cases, we have assumed that Marsh II-III were required. Not requiring Marsh II-III will automatically increase the prevalence of CD. In a subanalysis, we restricted our analysis to studies explicitly stating the use of Marsh III.

2.4 | Positive serology (endomysial or tissue transglutaminase antibodies)

In a post hoc analysis we also examined the prevalence of either biopsy-verified CD or positive antibodies. We did so since earlier research has shown that using serology to estimate prevalence of CD will yield higher values than defining CD solely according to small intestinal biopsy findings.[21] Positive serology was more frequent than biopsy-verified CD in four studies already included in the main analysis.[12,15,17,19] For this post-hoc analysis we also included an additional four studies without data on biopsy-verified CD.[22-25] Data on positive serology from the Agardh paper was calculated from data in their Table 2 (using a tissue transglutaminase of 17, and deducing seropositivity rate of 1.9%).[22] For the weighting of the meta-analysis we used 425 as the denominator. In addition, we

TABLE 2 Subgroup analysis of prevalence of coeliac disease in osteoporotic patients

Subgroup	Coeliac disease prevalence (%) (95% CI)	*P* value	Number of studies included
Overall prevalence	1.6 (1.1%-2.0%)	0.111[a]	8
Prevalence by age			
Individuals tested at <60 y	1.8 (1.3%-2.3%)	0.147[b]	4
Individuals tested at ≥60 y	1.0 (0.1%-1.9%)		4
Prevalence by geographic area			
Europe	1.7 (1.1%-2.2%)	0.562[b]	5
Outside of Europe	1.4 (0.6%-2.2%)		3
Prevalence based on gender			
Females only	2.3 (0.8%-3.7%)	0.324[b]	2
Females and males	1.5 (1.0%-2.0%)		6
Prevalence in studies with consecutively enrolled patients	1.8 (1.3%-2.2%)	0.013[b,c]	7
Prevalence based on antibody testing	1.6 (1.2%-2.0%)	<0.001[a]	12
Prevalence confirmed with Marsh III on biopsy	2.0 (1.5%-2.6%)	0.017[b]	4
Prevalence when all antibody-positive patients were biopsied	1.5 (0.8%-2.2%)	0.792	4

[a]Between individual studies.
[b]Between subgroups.
[c]Tested heterogeneity between the Legroux-Gerot et al[20] study vs all other studies (which enrolled patients consecutively).

included seropositivity rates from Drummond et al (1.2%)[23]; Kavuncu et al (0.7%)[24]; and Khoshnood et al (4.0%).[25]

2.5 | Osteoporosis

We a priori used the WHO definition of osteoporosis (>2.5 SD below the mean bone mineral density).[26] Details on osteoporosis determination, and bone mineral density measurements are given in Table S1. All included studies used DEXA to determine bone mineral density. All studies were graded using the Munn et al critical appraisal tool for prevalence studies[27] (see Table S2 for detailed results).

2.6 | Data items and risk of bias

We extracted data on (1) year of publication, (2) age at screening (<60 years vs ≥60 years), (3) country, and (4) Marsh stage.[28]

Since the underlying prevalence of CD differs between countries,[29] we compared the prevalence of CD in osteoporosis with that of the underlying CD prevalence in each country (Italy[30]; US[31]; UK[30]; Iran[32]; Brazil[33]; India: Sood et al cited through Cummins et al[34]; Czech Republic (we used data from neighbouring Hungary[35]); Argentina[36]; Ireland (we used UK data[30]) and France[37]).

2.7 | Summary measures, analysis method and heterogeneity

We used a fixed effect model to calculate the weighted prevalence of CD in individuals with osteoporosis to avoid undue influence on the summary estimate from smaller and less precise studies.[38] In a sensitivity analysis, data were also examined using a random effect model. Prevalence was reported with 95% confidence intervals (CI). Furthermore, we calculated heterogeneity (*I* squared, I^2).

One way to explore heterogeneity is to examine CD prevalence in subgroups. We compared the prevalence of CD in osteoporotic patients from Europe as opposed to other continents. In sensitivity analyses, we also excluded the paper by Fojtik et al[12] (the study with the largest number of patients) to see if this omission would influence the results. We also compared studies that included exclusively women with those including men, as a number of studies were limited to osteoporosis in postmenopausal women.

Finally, we used meta-regression to test the association between (1) age at time of testing for CD, (2) proportion of females, (3) publication year, and (4) underlying CD prevalence. Such factors may explain why studies show varying prevalence of CD in osteoporosis.

2.8 | Statistics software

We used STATA (StataCorp LLC, 4905 Lakeway Drive College Station, Texas 77845, USA) 13 for all analyses.

3 | RESULTS

Titles and abstracts were read for 1342 papers and 23 papers were identified as potentially relevant for this systematic review (disagreement was solved through consensus). These 23 papers were read in detail by ML, SM and JFL. Of these we excluded 15 papers due to no information on osteoporosis (n = 1),[39] the study of osteopenia or potential osteopenia (n = 4),[10,40-42] lack of data on biopsy for CD (n = 6),[22,24,25,43-45] high risk of selection bias (n = 2)[11,46] or lack of clarity regarding the absolute numbers of CD patients (n = 2).[23,47]

Our literature review identified eight relevant studies with a total of 3188 individuals with osteoporosis.[12,13,15-20] Of these, 59 (1.9%) had CD. The median prevalence of CD in all the included studies was 2.0%. The relevant studies are presented in Table 1. Visual inspection of a funnel plot analysis did not indicate any substantial publication bias (see Figure S2).

3.1 | Prevalence of CD in osteoporosis

We found a pooled prevalence of CD in osteoporosis of 1.6% (95% CI = 1.1%-2.0%; Figure 1). The heterogeneity (I^2) of our data was 40.1%. We examined this heterogeneity through a number of subgroup analyses.

When examining individuals with osteoporosis according to age at time of testing for CD, CD was somewhat higher in individuals

tested at <60 years of age[12,13,18,19] (1.8%; 1.3%-2.3%), as compared to those ≥60 years[15-17,20] (1.0%; 0.1%-1.9%; Table 2). Nonetheless, a meta-regression analysis found no continuous relationship between age at testing and CD prevalence (P = 0.917).

Coeliac disease was diagnosed in 1.7% (1.1%-2.2%) of osteoporotic patients tested in Europe[12,16-18,20] as opposed to 1.4% (0.6%-2.2%) tested outside of Europe (Table 2).[13,15,19] The prevalence of CD was 2.3% (0.8%-3.7%) in studies restricted to women,[16,17] and 1.5% (1.0%-2.0%) in studies that included men (Table 2).[12,13,15,18-20] A meta-regression found no statistically significant association between proportion of females and CD prevalence (P = 0.582).

Since CD has increased over time in several countries,[48,49] we explored the association between CD prevalence and osteoporosis according to year of CD testing, but found no association with year of testing (P = 0.115).

In one of the studies[20] it was unclear if patients had been included consecutively. When excluding this study, the pooled prevalence in the remaining studies was 1.8% (95% CI = 1.3%-2.2%; Table 2). Omitting the largest study (Fojtik et al[12]), the pooled prevalence was 1.3% (95% CI = 0.7%-1.9%).

When we required confirmation of CD through Marsh stage III on biopsy (and when this use of Marsh III was clearly stated in the paper[12,17-19]), the prevalence was 2.0% (95% CI = 1.5%-2.6%; Table 2). Restricting our analysis to studies where all antibody-positive individuals had been biopsied[13,15,18,19] did not influence the CD prevalence in osteoporosis (1.5%; 95% CI = 0.8%-2.2%) (Table 2).

Finally, we examined if the underlying CD prevalence in the general population influenced the CD prevalence of individuals with osteoporosis. There was a positive association between underlying CD prevalence in the general population and prevalence of CD in osteoporosis (Figure 2; P = 0.023).

Using a random effect model yielded a pooled prevalence of 1.6% (95% CI = 0.9%-2.2%; Figure S3).

3.2 | Prevalence of CD or positive tissue transglutaminase/endomysial antibodies in osteoporosis

In a post hoc analysis where an additional four studies which did not require biopsy for CD diagnosis were included (n = 814),[22-25] the prevalence of CD in osteoporosis was 1.6% (95% CI = 1.2%-2.0%; Table 2).

4 | DISCUSSION

This systematic review, based on 3188 individuals with osteoporosis, found a CD prevalence of 1.6%, corresponding to 1 in 62 patients with osteoporosis. The largest study[12] identified CD in 30/1584 (1.9%) osteoporotic patients. Importantly, the prevalence of CD did not change when we included studies based on positive CD serology (the absolute proportion went from 1.9% to 2.6% but the pooled weighted prevalence remained at 1.6%). It is likely that the pooled serological prevalence was not higher due to the inclusion of the studies by Drummond et al and Kavuncu et al, both of which demonstrated low prevalence figures (1.2% and 0.7%, respectively).[23,24]

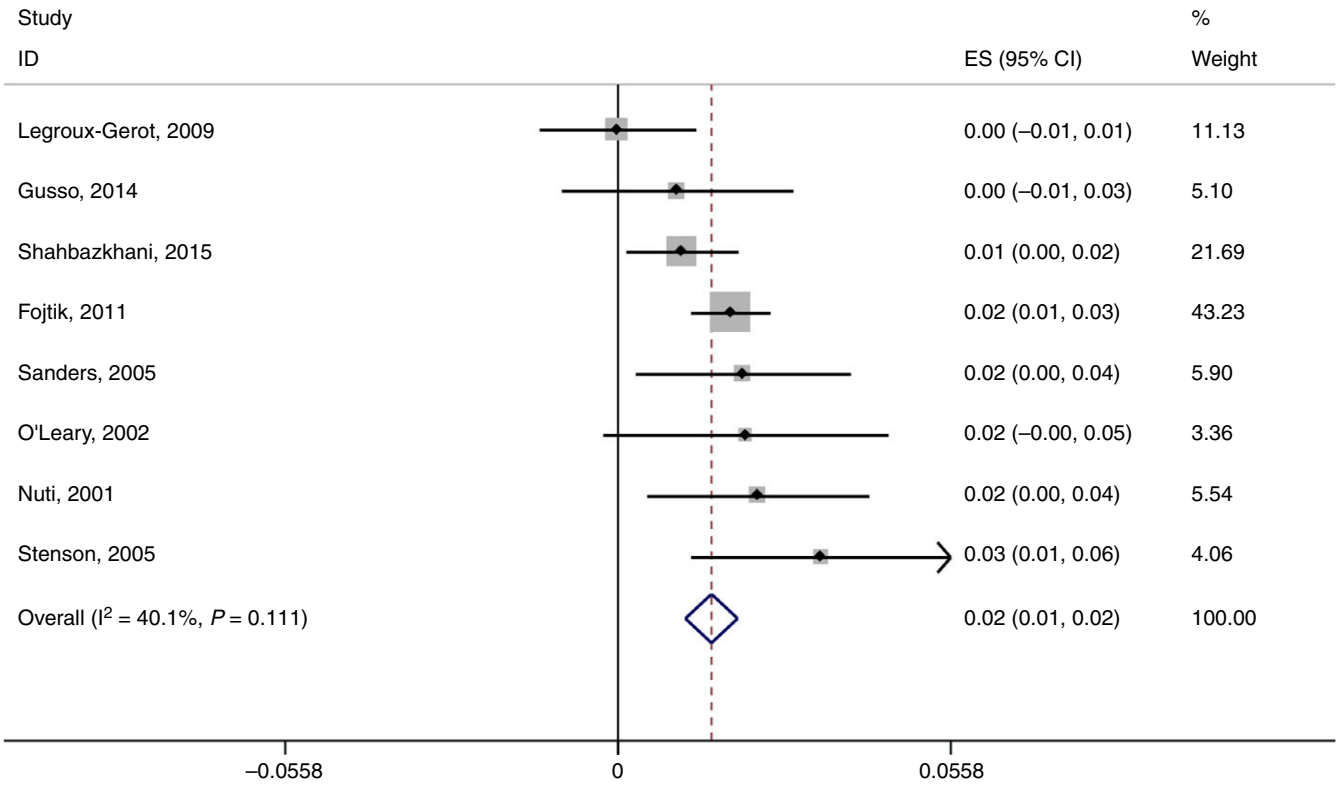

FIGURE 1 Prevalence of biopsy-verified coeliac disease in osteoporosis

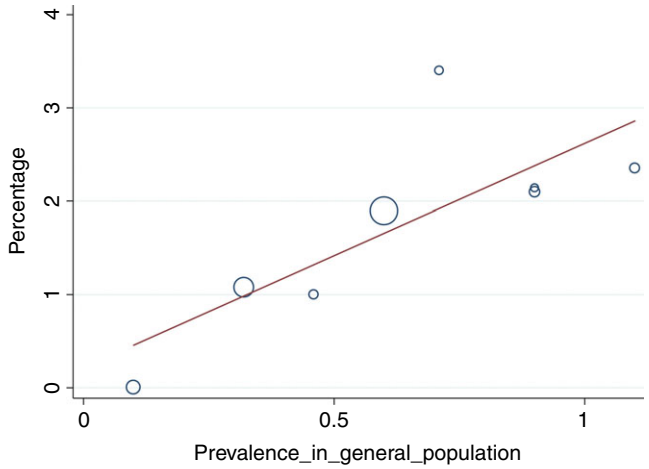

FIGURE 2 Meta-regression: Relationship between coeliac disease prevalence in the general population and among screened osteoporotic patients. *Y*-axis: Percentage of osteoporotic study participants with coeliac disease. *X*-axis: Prevalence of coeliac disease in the general population (P = 0.023)

4.1 | Osteoporosis and CD —general issues

As demonstrated by this paper, the prevalence of CD in osteoporosis is highly variable. Extremely high prevalence may be due to selection bias, if for instance only individuals with severe osteoporosis or osteoporosis with other symptoms indicative of CD are screened. We attempted to approach this problem by excluding studies where patient inclusion may not have been consecutive, but this did not change our prevalence estimates.

This study had a moderate heterogeneity. Despite a large number of subanalyses and meta-regressions, we found few explanations for the high heterogeneity, except that the CD prevalence in individuals with osteoporosis was dependent on the underlying prevalence in the general population (P = 0.023). We have previously demonstrated an increased risk of fractures in individuals with CD,[50] and that the risk of hip fracture is dependent on mucosal healing.[51] Furthermore, various studies have also shown that treatment with a gluten free diet improved bone mineral density in patients with CD.[52,53] Such studies suggest that treatment of CD is likely to decrease the excess fracture risk, and therefore a diagnosis of CD is probably beneficial to individuals with a history of fractures. In our Swedish follow-up study, we noted that the highest fracture incidence was during the last 2 years before (incidence rate ratio = 1.9) or first 2 years after CD diagnosis (incidence rate ratio = 3.0). Fracture incidence decreased and reached its lowest relative risk 10 years or more after CD diagnosis, most likely following the institution of a gluten-free diet (incidence rate ratio = 1.7).[50]

The mechanism for osteoporosis in individuals with CD is probably multifactorial. Individuals with CD often have a low bone density at diagnosis,[53,54] even in the absence of other symptoms or manifestations of CD.[54] This may be due to malabsorption of vitamin D and calcium resulting in secondary hyperparathyroidism.[55] Other factors include chronic inflammation,[56] with increased cytokine levels that interfere with bone growth[57] and autoimmune factors.[58,59] Skeletal fragility, as measured by microarchitecture by high-resolution computed tomography, is also diminished in individuals with newly diagnosed CD.[60] Improvement of bone density often occurs after institution of the gluten-free diet,[55,61,62] though the improvement can be modest.[63]

We explored a number of factors as possible predictors of higher CD prevalence in osteoporosis. Except for underlying CD prevalence in the population, none of them were linked to CD even though we had expected the prevalence to be higher in women (as autoimmunity is often more prevalent in women).

4.2 | Strengths and limitations

We did not restrict our analysis to English papers. In two instances,[12,47] we reviewed papers where only an English abstract was available provided that we were able to translate the text of the main paper. While there is little research on the effect on observational systematic review results from excluding non-English-language papers there are some data[64] (but not all[65]) suggesting that such exclusion could have an effect on the interpretation of trials.

We used two databases to ascertain studies on CD prevalence in individuals with osteoporosis (PubMed and EMBASE). Although we did not include unpublished data, the funnel plot (Figure S2) did not indicate any substantial publication bias. It has otherwise been shown in the study of antidepressants that exclusion of unpublished trials may overestimate the pooled effect of such drugs.[66] Although we used a large number of search terms to identify the studies in this paper, we cannot exclude that a number of fracture studies using none of these terms may have been missed.

We lacked data on severity of osteoporosis and its treatment, as well as on risk factors for fractures and postmenopausal state. A further limitation is that we had to use UK general population prevalence data as a surrogate for Irish data and Hungarian data as a surrogate for data from the Czech Republic when exploring if underlying CD prevalence could explain the varying prevalence of CD in studies on osteoporosis.

4.2.1 | Implications for screening

The British Society of Gastroenterology[67] guideline statement quotes the prevalence of CD in the general population as 0.25%-1%, depending on geographic area. The American College of Gastroenterology[68] quotes a prevalence of ~1%. The comparison of CD prevalence in osteoporosis and CD prevalence in the general population for specific countries from which studies were included in this meta-analysis can be seen in Figure 2.

Both the British Society of Gastroenterology[67] and, indirectly, the American College of Gastroenterology[68] recommend screening individuals with osteoporosis, while there is no evidence to suggest general mass screening.[69,70] In this study, we found that the CD prevalence in osteoporosis was not substantially higher than that in the general population. These findings argue against routinely screening patients with osteoporosis for CD, contrary with current guideline recommendations.

The fact that only one of our included studies had more than 1000 patients suggests that there is still a need for large-scale screening studies to explore the true prevalence of CD in osteoporosis, and to determine the utility of screening programs. One way to further increase the yield of such screening may be to limit screening to individuals with osteoporosis and additional symptoms of CD.

5 | CONCLUSION

In conclusion, we found a prevalence of CD of 1.6% in individuals with osteoporosis. Although there is an abundance of large-scale studies that have demonstrated an increased risk of fracture after CD diagnosis, there is a paucity of screening studies in individuals with confirmed osteoporosis. Such studies are needed and should be carefully designed, clearly outlining their criteria for both CD and osteoporosis to determine the utility of serological screening programs.

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AUTHORSHIP

Guarantor of the article: JFL.

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SUPPORTING INFORMATION

Additional supporting information will be found online in the Supporting Information section at the end of the article.

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