APPLICATION OF THE WHO FRACTURE RISK ASSESSMENT TOOL (FRAX®) TO PREDICT NEED FOR DEXA SCANNING AND TREATMENT IN PATIENTS WITH INFLAMMATORY BOWEL DISEASE AT RISK OF OSTEOPOROSIS.

James R Goodhand, Nikolaos Kamperidis, Huyenly Nguyen, Mahmood Wahed, David S Rampton

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APPLICATION OF THE WHO FRACTURE RISK ASSESSMENT TOOL (FRAX®) TO PREDICT NEED FOR DEXA SCANNING AND TREATMENT IN PATIENTS WITH INFLAMMATORY BOWEL DISEASE AT RISK OF OSTEOPOROSIS.

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<tr>
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<th><em>Alimentary Pharmacology &amp; Therapeutics</em></th>
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Kamperidis, Nikolaos; Barts and the London School of Medicine and Dentistry, Centre for Digestive Diseases, Blizard Institute of Cell and Molecular Science  
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Rampton, David; Royal London Hospital, Endoscopy Unit |
| Keywords: | Inflammatory bowel disease < Disease-based, Osteoporosis < Topics, Crohn’s disease < Disease-based, Ulcerative colitis < Disease-based |
Re: ‘APPLICATION OF THE WHO FRACTURE RISK ASSESSMENT TOOL (FRAX®) TO PREDICT NEED FOR DEXA SCANNING AND TREATMENT IN PATIENTS WITH INFLAMMATORY BOWEL DISEASE AT RISK OF OSTEOPOROSIS’

Dear Jean-Frederic,

Please find enclosed our revised manuscript and responses to the reviewer’s comments. For convenience and ease of reading we include here the reviewer’s comments first (in bold text), and then our response (in regular text).

Reviewer: 1

Comments for Transmission to the Authors

I think the Summary must make it clear that the FRAX tool is WHO, and free. This has now been added to the abstract.

I wonder if the Authors can devise a figure, that lecturers would use, that demonstrates the results that are in Table 3, in an easily understood manner... quantifying how many DEXA scans and bisphosphonate treatments would be saved? In accordance with this request we have devised Figure 4 to supplement Table 3.

Reviewer: 2

Comments for Transmission to the Authors

This is an interesting paper which will be of interest to readers of AP&T. It appears to be the first study of the usefulness of using FRAX scores in IBD patients. There is considerable concern regarding osteoporosis in IBD patients however many of these patients are at low risk of fracture within the medium term even with a BMD in the osteoporotic range - mostly due to young age.
There is an argument that in the statistical analysis T-scores should not be compared as they are so probably acceptable.

We acknowledge this, but have already presented raw BMD data to accompany the T-scores in Table 2.

The main concern with this cohort is how representative they are of IBD patients in general - this is only lightly touched upon in the Discussion and this should be strengthened - the comment that the findings are generalisable is difficult to confirm.

There are some suggestions that the cohort is not typical of all IBD patients; most studies find that CD is more frequently associated with reduced BMD than UC, that age and disease duration are risks and often that use of steroid an independent risk factor. That these weren’t found may suggest that these patients were not generally representative and were selected for screening because they had more severe disease, especially UC where there is an overrepresentation of patients with pancolitis compared with community based studies.

We have re-structured the Discussion, with the sub-headings ‘Key Results’, ‘Limitations of FRAX in IBD’, and ‘Sources of bias’, to allow discussion of these points (and those raised below).

We acknowledge the likely (and deliberate) selection bias in our selection of patients perceived to be at risk and thus the limited validity of extrapolating conclusions from this group of patients to IBD ‘all-comers’. The term ‘generalisability’ has been removed.

There are BSG guidelines concerning screening for reduced BMD and it would be interesting to know how many of these patients met these criteria at the time of screening.

In brief, the BSG guidelines read ‘Without a reliable scoring system, common sense suggests that patients with the features shown in Boxes 1 and 2, such as age over 70, together with those with very active disease, those with disease responding poorly to treatment, and those with poor nutrition should be considered for DEXA. Those requiring steroids need special consideration’.

Where possible (see supplemental Table 1) we have completed the proportions with each of these factors in our dataset. Despite not having collected data on recent weight loss, physical activity, anticonvulsant use, oestrogen exposure, calcium exposure, visual acuity and neuromuscular disorders, overall only 2.6% (3/116) patients in our cohort did not fulfil at least one of these risk criteria. We now refer to this in the Discussion.

Another confounding not discussed is that many patients were taking a Ca/Vit D supplement and so this may have had an effect on BMD.

We include below the revised baseline demographics [supplemental table 2], the proportions of patients with low bone mineral density [supplemental table 3], and the FRAX scores (pre and post BMD inclusion) and recommended treatments compared with our current practice [supplemental table 4] for all the patients not on calcium and vitamin D.

Having excluded patients taking oral calcium and vitamin D supplements, the clinical FRAX® score alone, when compared to the FRAX score including the BMD result, had a sensitivity of 100% (95%CI: 60%-100%), specificity of 49% (95%CI: 35%-63%), positive predictive value of 24% (95%CI: 11%-42%) and negative predictive value of 100% (95%CI: 83%-100%) in identifying those patients with IBD needing BMD measurement (intermediate risk) or preventive therapy (high risk). Thus calcium and vitamin D, allowing for the reduction in sample size, has no major effect on the usefulness of FRAX.

It is mentioned that a weakness of FRAX scores is that it is dependent on BMI but it is also dependent on steroid usage for more than 3 months and so sustained use for this period would require a re-calculation of the score.

We acknowledge this important point in the Discussion. The FRAX score does not take into account steroid dose and duration. The major finding of this study is the application of the FRAX tool to determine the need for screening with DEXA scanning in IBD patients perceived to be at risk of osteoporosis. In practice, the FRAX tool in fact already recommends DEXA scanning for all patients of medium or smaller build who are on steroids, and who have a secondary cause of osteoporosis (IBD): as a result, the dose and duration of corticosteroid usage in influencing pre-DEXA FRAX score is irrelevant. When a DEXA scan has been done, the deleterious effects of high cumulative doses of corticosteroids (as opposed to use of any dose) will be reflected in a lower BMD and
incorporated in the post-DEXA FRAX score.

With these provisos the study suggests that a large number of DEXA scans (36%) in this cohort (with probably more severe disease than is typical) were not necessary. This has the potential for considerable reduction in costs. In addition the use of bisphosphonates was particularly poorly directed on the basis of fracture risk reduction; 9/11 who received them did not need them but 1/11 who did were not prescribed them. Individualising bone protection in IBD care has the potential for cost reduction, decreasing the risk of side effects in patients who are unlikely to benefit but maximising benefit to those who are at greatest risk of fracture.

We have incorporated this last point into the Conclusions.

These observations are important and seem to be novel and so I would recommend acceptance of this paper for AP&T despite the reservations about the cohort and it’s generalisability to all patients with IBD.

Reviewer: 3

Comments for Transmission to the Authors

1. Can the authors comment on some of FRAX’s limitations to IBD patients. For example, it does not account for duration and dose of corticosteroids. Also, it is dependent on clinicians identifying subclinical fractures, which in IBD patients can be as high as 20 percent (Heijckmann et al. Eur J Gastroenterol Hepatol 2008;20:740-47, Siffledeen et al. Clinical Gastro Hep 2007;5:721-8). It does not account for low BMD of areas other than the femoral neck. In IBD patients, low vertebral bone density may be a more important risk factor, given that IBD patients are younger and are not as prone to hip fracture (Vestergaard & Mosekilde. Am J Epidemiol 2002;156:1710, Vestergaard et al. Gut 2000;46:1761-81). Furthermore, in IBD, severity of vertebral deformities is a strong predictor of non-vertebral fracture risk (Delmas et al. Bone 2003;33:522-32).

As indicated above, we have re-structured the Discussion with the sub-headings ‘Key Results’, ‘Limitations of FRAX in IBD’, and ‘Sources of bias’. We now include paragraphs addressing the duration and dose of corticosteroids, and the importance of vertebral fractures in IBD and include these references.

2. There is a selection bias in that patients recruited for the study were only those deemed (by clinical judgement) to have risk factors for fracture. It neglects those patients who were not selected by the clinicians originally, who may have clinically silent risks and objectively still be at risk of fracture. This should be stated in the discussion.

This is now further emphasised in the Discussion.

3. In order to substantiate the predictive ability of FRAX in IBD, it should also accurately predict those (clinically pre-determined) low-risk patients not requiring testing/treatment. Such a cohort of patients at low-risk for fracture, having undergone DEXA, had not been identified in this study. Is it possible for the authors to identify (and incorporate into the analysis) IBD patients who were not considered high risk for osteoporosis, but who underwent DEXA?

We acknowledge this important point in the Discussion. Unfortunately in our population only 3 patients were identified with no risk factors (see above) according to the current BSG guidelines. We have no data on the applicability of this tool in patients perceived by our clinicians as being at low risk, and unfortunately we cannot justify prospective use of DEXA scanning, for reasons of both ethics and cost (approx 300 euros/DEXA scan, or 30000 euros for 100 low risk patients), to obtain such information.

4. Findings of the Fracture Intervention trial studied the ability of FRAX to predict vertebral fractures in the general population > 40. Briefly, although FRAX (with or without femoral neck BMD) did predict vertebral fractures, the strongest predictor of future vertebral fracture was the presence of vertebral fracture at baseline. These findings may be useful for comment in the current study, given that IBD patients have a high prevalence of vertebral deformities, which are not captured in the FRAX tool (Donaldson et al, JBMR 2009.24:1793-99).

This is important. Interestingly, the BMD at the lumbar spine in our cohort of patients was significantly lower than in the femoral spine. We have now included this and these references in the Discussion.
5. The authors did collect an impressive array of data, including cumulative corticosteroid use, calcium and vitamin D supplementation, etc. Could the authors comment on the influence of results if those patients taking vitamin D/calcium supplements were excluded from the analysis?

See comments above regarding calcium supplements.

We very much hope that the changes we have made to the manuscript make it acceptable for publication.

Best wishes

Yours sincerely,

David Rampton
Prof Clinical Gastroenterology
d.rampton@qmul.ac.uk

REFERENCES

## APPENDIX: SUPPLEMENTAL TABLES

**BOX 1**

<table>
<thead>
<tr>
<th>High risk (RR&gt;2) Non-modifiable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Older age (&gt; 70 years)</td>
</tr>
<tr>
<td>Prior osteoporotic fracture</td>
</tr>
</tbody>
</table>

**High risk (RR>2) Modifiable**

| Low body weight (BMI <20 – 25 kg/m2 or weight <40 kg) | 32 (27.6%) |
|------------------------------------------------------|
| Weight loss (greater than 10%) | Not recorded |
| Physical inactivity | Not recorded |
| Use of corticosteroids | 62 (53.3%) |
| Use of anticonvulsants | Not recorded |

<table>
<thead>
<tr>
<th>Moderate risk (RR 1-2) Non-modifiable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
</tr>
<tr>
<td>Untreated early menopause (&lt;45)</td>
</tr>
<tr>
<td>Late menarche (&gt;15)</td>
</tr>
<tr>
<td>Short fertile period (&lt;30 years)</td>
</tr>
<tr>
<td>Family history of osteoporotic fracture</td>
</tr>
</tbody>
</table>

**Modifiable**

| Smoking | 19 (16.4%) |
| Low calcium intake | Not recorded |

**BOX 2**

<table>
<thead>
<tr>
<th>Non-modifiable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Older age</td>
</tr>
<tr>
<td>Prior osteoporotic fracture</td>
</tr>
<tr>
<td>Family history of hip fracture</td>
</tr>
<tr>
<td>Poor visual acuity*</td>
</tr>
<tr>
<td>Neuromuscular disorders*</td>
</tr>
</tbody>
</table>

**Modifiable**

| Low body weight | 32 (27.6%) |
| Use of corticosteroids | 62 (53.3%) |
| Cigarette smoking | 19 (16.4%) |
| Alcohol excess | 5 (4.3%) |

**Table 1: Proportion of patients at risk for osteoporosis according to BSG criteria.**
Table 2: Baseline demographic characteristics of patients that were considered to be at risk of osteoporosis at the time of the DEXA scanning. Patients who were on calcium/vitamin D supplementation at the time of DEXA scanning have been excluded. *, initiated after DEXA scanning

T-scores of: ≥ -1 were considered as corresponding to normal BMD. T-scores < -1 were considered as corresponding to low BMD
Table 3: Prevalence of reduced bone mineral density (BMD) measured at the lumbar spine and femoral neck in Crohn’s disease and UC. Patients who were on calcium/vitamin D supplementation at the time of the DEXA scanning have been excluded. T-scores of ≥ -1 were considered normal; -1 and -2.5 osteopaenic; ≤ -2.5 as osteoporosis, were used to categorise BMD except in 13 patients under 20, when Z scores were used. T-scores were significantly lower at the spine than the hip (p<0.01).

<table>
<thead>
<tr>
<th>DEXA Site</th>
<th>UC (16)</th>
<th>Crohn’s (43)</th>
<th>p - value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lumbar spine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean BMD [SEM]</td>
<td>0.97 [0.04]</td>
<td>0.97 [0.02]</td>
<td>0.89</td>
</tr>
<tr>
<td>Mean [SEM] Z score</td>
<td>-0.59 [0.33]</td>
<td>-0.53 [0.21]</td>
<td>0.88</td>
</tr>
<tr>
<td>Mean [SEM] T score</td>
<td>-0.94 [0.32]</td>
<td>-0.94 [0.20]</td>
<td>0.99</td>
</tr>
<tr>
<td>Osteopaenia n (%)</td>
<td>6 (37.5%)</td>
<td>15 (34.5%)</td>
<td></td>
</tr>
<tr>
<td>Osteoporotic n (%)</td>
<td>2 (12.5%)</td>
<td>6 (14%)</td>
<td>0.98</td>
</tr>
<tr>
<td>Femoral neck</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean BMD [SEM]</td>
<td>0.94 [0.04]</td>
<td>0.89 [0.02]</td>
<td>0.32</td>
</tr>
<tr>
<td>Mean [SEM] Z score</td>
<td>-0.14 [0.23]</td>
<td>-0.40 [0.14]</td>
<td>0.32</td>
</tr>
<tr>
<td>Mean [SEM] T score</td>
<td>-0.41 [0.25]</td>
<td>-0.71 [0.14]</td>
<td>0.29</td>
</tr>
<tr>
<td>Osteopaenia n (%)</td>
<td>5 (31.3%)</td>
<td>20 (46.5%)</td>
<td></td>
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<tr>
<td>Osteoporotic n (%)</td>
<td>0 (0%)</td>
<td>1 (2.3%)</td>
<td>0.44</td>
</tr>
<tr>
<td>NOGG risk stratification</td>
<td>n (%)</td>
<td>BMD t-score mean [SEM]</td>
<td>Pre-BMD inclusion FRAX® (%) mean [SEM]</td>
</tr>
<tr>
<td>--------------------------</td>
<td>-------</td>
<td>-------------------------</td>
<td>----------------------------------------</td>
</tr>
<tr>
<td>Low (No treatment)</td>
<td>25 (42.4%)</td>
<td>S: -0.86 [0.28]</td>
<td>M 3.9% [0.19]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>FN: -0.63 [0.12]</td>
<td>H 0.4% [0.06]</td>
</tr>
<tr>
<td>Intermediate (Measure BMD)</td>
<td>23 (39%)</td>
<td>S: -0.99 [0.26]</td>
<td>M 8.7% [0.99]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>FN: -0.67 [0.2]</td>
<td>H 2.1% [0.58]</td>
</tr>
<tr>
<td>High (Consider treatment)</td>
<td>11 (18.6%)</td>
<td>S: -1.03 [0.38]</td>
<td>M 15.2% [3.41]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>FN: -0.79 [0.3]</td>
<td>H 4% [1.44]</td>
</tr>
</tbody>
</table>

Table 4: FRAX scores (pre and post BMD inclusion) and the recommended treatment compared with our current practice. Patients on calcium/vitamin D supplementation at the time of the DEXA scanning have been excluded. Patients have been stratified by risk (low, intermediate or high) according to the pre-BMD FRAX® score. † Paired data were compared using students paired t-test. ‡ Treatment recommendations were compared to current use of bisphosphonates using Chi-squared analysis. S, denotes spine; FN, femoral neck; M, major; H, Hip.
Application of the FRAX® tool in patients with IBD at risk of osteoporosis.

Title: APPLICATION OF THE WHO FRACTURE RISK ASSESSMENT TOOL (FRAX®) TO PREDICT NEED FOR DEXA SCANNING AND TREATMENT IN PATIENTS WITH INFLAMMATORY BOWEL DISEASE AT RISK OF OSTEOPOROSIS.

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Short title: Application of the FRAX® tool in patients with IBD at risk of osteoporosis.

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Keywords
Ulcerative colitis
Crohn’s disease
Osteoporosis
Fracture risk assessment
Application of the FRAX® tool in patients with IBD at risk of osteoporosis.

ABSTRACT

Background: Although patients with inflammatory bowel disease (IBD) are at increased risk of osteoporosis, low bone mineral density (BMD) alone confers only a modest increase in risk of fracture. The FRAX® score, developed by the WHO, is a free web-based clinical scale assessing the 10-year fracture risk and need for lifestyle advice/reassurance, DEXA scanning or preventive treatment.

Objectives: To assess the accuracy of pre-BMD FRAX scores in identifying at risk IBD patients needing BMD measurement (intermediate risk) and/or therapy (high risk).

Methods: We retrospectively calculated FRAX scores in 116 consecutive IBD outpatients (81 Crohn’s disease, 35 ulcerative colitis) having DEXA scans in 2005-2009 because they were considered at risk of osteoporosis.

Results: On DEXA scans, 47% [38/81] and 12% [10/81] patients with Crohn’s disease were osteopaenic and osteoporotic, respectively; equivalent figures for patients with UC were 34% [12/35] and 14% [5/35]. The clinical FRAX® score alone, when compared to the FRAX score including the BMD result, had a sensitivity of 100% (95%CI: 70%-100%), specificity of 40% (95%CI: 31%-50%), positive predictive value of 16% (95%CI: 9%-27%) and negative predictive value of 100% (95%CI: 90%-100%) in identifying those patients needing BMD measurement (intermediate risk) or preventive therapy (high risk).

Conclusions: In patients with IBD perceived to be at risk of osteoporosis and/or osteopaenia, the clinical FRAX score alone can accurately predict the risk of osteoporotic fracture and thereby reduce the need for DEXA scans and unnecessary anti-osteoporosis treatment.
Application of the FRAX® tool in patients with IBD at risk of osteoporosis.

INTRODUCTION

In the general population, the majority of fragility fractures occur in patients with bone mineral densities (BMD) in the osteopaenic rather than osteoporotic range, suggesting that factors other than BMD need to be taken into account when determining both the need for screening and anti-osteoporosis treatment. In keeping with this, while patients with IBD are at increased risk of osteoporosis, low BMD itself confers only a modest increase in the risk of fracture such that routine screening with dual x-ray absorptiometry (DEXA) scanning is not justified according to recent British Society of Gastroenterology and American Gastroenterological Association guidelines.

Based on data from population-based cohorts, the World Health Organisation (WHO) have developed a web-based fracture risk assessment tool (FRAX®), that integrates an individual’s risk factors and reports the 10-year probability of hip or other major osteoporotic fracture (clinical spine, forearm, hip or shoulder fracture). It divides the level of risk into high, intermediate and low and can be calculated with or without BMD score. Using guidelines from the National Osteoporosis Guidelines Group (NOGG) the online tool recommends the need for treatment, DEXA scanning or lifestyle advice/reassurance.

In an attempt to prevent unnecessary DEXA scanning and anti-osteoporotic therapy, we aimed to assess the accuracy of pre-BMD FRAX scores in identifying those patients with IBD needing BMD measurement (intermediate risk) and/or preventive therapy (high risk) with and without DEXA scan.

METHODS

Study design and setting

We conducted a retrospective evaluation of the FRAX® tool in adult patients (age≥20) screened for low BMD with DEXA scanning at Barts and the London NHS Trust from 2005-2009.

IBD Participants

Patients attending our specialist IBD out-patient clinics with an established diagnosis of IBD whose clinicians considered them to be at risk of osteoporosis and who had therefore had a
Application of the FRAX® tool in patients with IBD at risk of osteoporosis.

DEXA scan between 2005 and 2009 were eligible for inclusion. In those patients who had duplicate scans to monitor BMD (n=29), only the results of the first scan were included. Because we were interested in anti-osteoporosis prescribing based on BMD results alone we excluded patients (n=15) taking bisphosphonates before 2005, after the current DEXA scanner was installed (see below).

Using electronic case note review, cross-sectional data including demographics, disease type, duration, activity and extent according to the Montreal classification, therapies, including cumulative dose of corticosteroids in the preceding three years, and previous surgery at the time of scanning were determined. Disease activity at the time of scanning was recorded and defined for Crohn’s disease as abdominal pain and/or diarrhoea with a CRP>10mg/ml, and for UC as diarrhoea with rectal bleeding.

Bone mineral density measurement

All patients underwent DEXA scanning using the same Hologic Discovery A scanner (system number 80933), installed at St Bartholomew’s Hospital in 2004. We used WHO guidelines to define bone mineral density: a T-score of ≥ -1 denotes normal bone; a T-score between -1 and -2.5 denotes osteopaenia, and a T-score of ≤ -2.5 denotes osteoporosis.

FRAX score

FRAX® scores were calculated with the online tool using the UK algorithm\textsuperscript{15,19}. In brief, this requires the completion of 12 fields: age (years); sex (male or female); height (cm); weight (kg); history of minimal trauma fracture (defined as a fracture in adult life occurring spontaneously, or arising from trauma which, in a healthy individual, would not have resulted in a fracture); history of parental hip fracture; corticosteroid exposure (defined as more than 7.5mg prednisolone [or equivalent] in the preceding three months); a concomitant diagnosis of rheumatoid arthritis; a secondary cause of osteoporosis; daily alcohol intake of more than 3 units and whether they smoked or not at the time of the scan. All patients were considered to have a secondary cause of osteoporosis (namely, IBD). Data on personal and family history of fracture, rheumatoid arthritis, alcohol and smoking habits were confirmed by telephone interview.

FRAX® scores were calculated and patients’ risk stratified using the age-adjusted NOGG recommendations on the basis of clinical factors alone; FRAX scores were then re-determined with BMD (g/cm\textsuperscript{2}) included\textsuperscript{19}.
Application of the FRAX® tool in patients with IBD at risk of osteoporosis.

Statistical methods

Statistical analyses were conducted using SPSS (version 16) and Prism (version 4) software. All analyses were two tailed and p values <0.05 considered significant. Univariate analysis of baseline demographic data comparing those IBD patients with normal BMD and those who were osteoporotic or osteopaenic was carried out using chi-squared test for categorical data and Student’s t-test for continuous variables. Paired FRAX® scores within risk groups were compared using paired Student’s t test, and sensitivity analyses were undertaken to determine the accuracy of pre-BMD NOGG recommendations with those after the BMD was taken into account for the need for screening with DEXA scanning. Finally, NOGG treatment recommendations were compared with our patients’ current treatments based on BMD alone using Chi-squared analysis.

Ethical Consideration

Because we were evaluating the appropriateness of use of results of DEXA scans already completed in our IBD service, we did not require formal ethical approval according to the guidelines of the UK National Research Ethics Service (NRES).

RESULTS

We identified 178 IBD outpatients who had had DEXA scans between 2005 and 2009. The telephone questionnaire response rate to determine the FRAX® score was 72% giving a study population of 116 patients (Figure 3).

Baseline demographics in relation to bone mineral density

There were no significant differences between those patients with normal or low (t-scores ≤ -1, i.e BMDs in the osteopaenic and osteoporotic range) BMD in terms of gender, ethnicity, disease type, duration, location, extent, behaviour and/or activity (Table 1). Similarly, there was no difference in the proportions of patients treated with corticosteroids, 5 aminosalicylates, immunosuppressants, or monoclonal antibodies against tumour necrosis factor (anti-TNFs). No difference was seen in the cumulative mean [SEM] dose of prednisolone between groups (normal BMD 1242 [331]mg vs low BMD 1437 [274]mg p=0.77). The number of patients on calcium/vitamin D preparations was significantly higher in the low BMD group for both UC and CD (Table 1).
Overall, 47% [38/81] patients with Crohn’s disease and 34% [12/35] patients with UC were osteopaenic, and 12% [10/81] Crohn’s patients and 14% [5/35] UC patients were osteoporotic at either the femoral head or lumbar spine. There was a strong positive correlation between the t-score measured at the femoral neck and at the lumbar spine (R=+0.66 [0.55, 0.75] 95%CI); the mean t-score was significantly lower at the lumbar spine compared with the femoral neck for both Crohn’s and UC (Table 2).

Frax® scores with and without BMD measurement: sensitivity analysis

According to clinical FRAX® scores alone, 36% (42/116) of patients were at low risk for fracture, 47% (55/116) at intermediate risk and 16% (19/116) at high risk. Although there was a trend for the measured t-scores to decrease with increasing FRAX risk this was not statistically significant (Table 3). The mean FRAX® scores in each of the three risk groups fell significantly in all groups for both major and hip fractures following the inclusion of BMD scores (Table 3).

Overall, the clinical FRAX® score alone, when compared to the FRAX score including the BMD result, had a sensitivity of 100% (95%CI: 70%-100%), specificity of 40% (95%CI: 31%-50%), positive predictive value of 16% (95%CI: 9%-27%) and negative predictive value of 100% (95%CI: 90%-100%) in identifying those patients with IBD needing BMD measurement (intermediate risk) or preventive therapy (high risk).

Indications for anti-osteoporosis treatment

On the basis of their BMD alone and as part of our routine practice, eleven patients were started on treatment for osteoporosis with a bisphosphonate following their DEXA scan. In this small group of patients, there was no significant difference between our existing practice and that suggested by NOGG (post BMD inclusion) in the 97 patients at low or intermediate risk for fracture (Table 3). However, according to the NOGG guidance, 9 of these 97 patients were being treated unnecessarily.

Moreover, in the high risk group, while treatment was recommended by NOGG in 11/19 (58%) patients, only 1 patient was being treated with a bisphosphonate (p<0.01).
DISCUSSION

Key results

In keeping with the existing literature, our patients with IBD, on the basis of their t-scores, had lower BMDs than the general population. In patients with IBD who are perceived by their clinicians as being at increased risk of osteoporosis and/or osteopaenia, the clinical criteria alone of the FRAX® score can be used to predict those patients who need DEXA scans and/or consideration for specific treatment of osteoporosis. In our series of 116 such patients, by using this score over 5 years we could have prevented 36% DEXA scans. Our data also suggest that patients who carry a high clinical risk of fracture are frequently not considered for treatment when this decision is based on t-scores alone. Furthermore, according to NOGG, 8% of our patients were over-treated with bisphosphonates.

Limitations of FRAX® in IBD patients

There are some limitations to these conclusions. First, the FRAX® algorithms are based on general population cohort studies undertaken in people over the age of 40, and have not been validated in IBD populations. The FRAX® tool calculates risk for patients under the age of 40 using data for individuals aged 40. Data for people under the age of 40, particularly in IBD-specific populations, is unlikely to be available for several decades, since in order for enough fractures to occur to determine actual risk, prospective cohort studies in young patients will take 30 - 60 years to complete. It is likely that the fracture risk in the 69 (59%) of our subjects who were under 40 was over-estimated, because of age-related loss in BMD.

Second, body mass index, a component of the FRAX® score, does not fluctuate as much in the general population as it does in IBD, where periods of active disease may precipitate substantial weight loss. In order to avoid over-estimating the fracture risk in IBD, it may therefore be best to complete the FRAX® score during periods of remission: in our group about a third of our patients had active disease at the time of scanning.

Third, although the FRAX® tool includes corticosteroids as a dichotomous risk factor, it does not take into account dose or duration of exposure to steroids. In practice, the FRAX tool in fact already recommends DEXA scanning for all patients of medium or smaller build who are on steroids, and who have a secondary cause of osteoporosis (IBD): as a result, the dose and duration of corticosteroid usage is irrelevant as a potential influence on pre-DEXA FRAX
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score. When a DEXA scan has been done, the deleterious effects of high cumulative doses of corticosteroids (as opposed to use of any dose) will be reflected in a lower BMD and incorporated in the post-DEXA FRAX score.

Potential Sources of Bias

When evaluating the validity of extrapolation of our results to other IBD populations, three potential sources of bias need to be considered.

First, because the data was collected by retrospective electronic case-note review and a telephone interview, the data is subject to discrepancies in interpretation, missing data, and recall bias, in particular for cigarette smoking and alcohol consumption, and it is possible that because of these factors the FRAX® scores were underestimated.

Second, the patients included were selected deliberately because they were perceived by their treating clinicians to be at risk of osteoporosis and had for that reason had a DEXA scan arranged. In this context, however, only 2.6% (3/116) patients would not have fulfilled the current BSG criteria for DEXA screening (data not shown)\(^1\). We have no data on the applicability of this tool in patients perceived as being at low risk: unfortunately we cannot justify prospective use of DEXA scanning to obtain such information on ethical grounds and for reasons of cost (approximately €300/DEXA scan, or €30000 for 100 low risk patients). Conversely, it is not known what proportion of patients in a consecutive cohort of unselected IBD patients would be scored as being at intermediate and/or high risk based on a pre-DEXA FRAX test, and thus the service implications and costs in terms of DEXA screening that such an approach would create.

As a result of a deliberate patient selection policy, our cohort is characterised by patients with a tendency towards extensive and severe disease, which probably accounts for the lack of differences seen in the univariate analyses between patients with normal and low BMDs (Table 1) that have been reported in previous prospective studies of IBD patients, for example, in disease duration\(^{21-24}\) and steroid exposure\(^{25-27}\). In addition, about half of our patients were taking calcium and vitamin D supplements. Sub-analyses (data not shown) of patients taking and not taking calcium and vitamin D supplements showed that they had little effect on BMD and did not alter the usefulness of the pre-DEXA FRAX score as a screening tool in these patients.
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Compared with the general population, patients with IBD are more prone to vertebral than hip fractures. In keeping with this observation, t-scores were significantly lower at the lumbar spine than at the femoral neck in our patients. Although FRAX® (with or without femoral neck BMD) predicts vertebral fractures in the general population, the strongest risk factor for future vertebral fracture in Donaldson’s study was the presence of a vertebral fracture at baseline. Because vertebral fractures can be asymptomatic, they are frequently overlooked by both patients and clinicians: subclinical fractures reportedly occur in up to 20% IBD patients. It is likely then that in a proportion of our patients, the FRAX® scores may have underestimated the risk of subsequent fracture.

Conclusions

Although patients with IBD are at risk for low bone mineral density this confers only a small increase in the risk of fragility fracture. The web-based WHO FRAX® tool is a readily available, easy to use, free and rapid way of assessing fracture risk based on clinical factors alone that could be utilized in IBD outpatient clinics to predict those patients who need DEXA scans and/or consideration for specific treatment of osteoporosis. If the patient is at low risk then no DEXA scan is required. If the FRAX® score based on clinical risk factors alone is intermediate and/or high then patients should undergo DEXA scanning and once the BMD is known the FRAX® score recalculated to determine the need for specific anti-osteoporosis treatment. Individualizing bone protection using the FRAX® score in IBD care has the potential to reduce the cost related to DEXA scanning; it may also obviate the risk of side effects in patients who are unlikely to benefit from treatment, and ensure appropriate treatment for those who are at greatest risk of fracture.

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All authors approved the final manuscript, and declare no financial conflict of interest. JRG conceived the study, collected and analysed the data and prepared the manuscript. HN, NK, and MW participated in study design, collected and analysed the dataset. DSR participated in study design, interpretation of its results and preparation of the manuscript. We are grateful to Dr James Lindsay and Dr Louise Langmead, for their constructive criticism whilst reviewing the work and for allowing us to include their patients. We would also like to thank the National Association of Crohn’s and Colitis and CORE/British Society Paediatric Gastroenterology and Nutrition (BSPGHAN) for funding JRG’s research.
Table 1: Baseline demographics of patients considered to be at risk for osteoporosis at the time of DEXA scanning.
T-scores of ≥ -1 were considered as corresponding to normal BMD. T-scores < -1 were considered as corresponding to low BMD.

Table 2: Prevalence of reduced bone mineral density (BMD) measured at the lumbar spine and femoral neck in Crohn’s disease and UC. T-scores of ≥ -1 were considered normal; -1 and -2.5 osteopaenic; ≥ -2.5 as osteoporosis were used to categorise BMD except in 13 patients under 20, when Z scores were used. T-scores were significantly lower at the spine than the hip (p<0.01).
Table 3: FRAX® scores (pre and post BMD inclusion) and the recommended treatment compared with our current practice. Patients have been stratified by risk (low, intermediate or high) according to the pre-BMD FRAX® score. † Paired data were compared using Students paired t-test, ‡ Treatment recommendations were compared to current use of bisphosphonates using Chi-squared analysis. S, denotes spine; FN, femoral neck; M, major; H, Hip.
REFERENCES


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\textbf{FIGURE 1a:} WHO case finding strategies, adapted from Kanis JA on behalf of the World Health Organization Scientific Group (2008) \textsuperscript{16}. 
FIGURE 1b. NOGG age-related treatment thresholds without BMD inclusion into the FRAX® score, adapted from 15.
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FIGURE 3: Study overview using STROBE criteria.32
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Figure 4. Comparison of the post-DEXA NOGG recommendations and clinical practice at Barts and The London NHS Trust (BLT) in the low, intermediate and high risk groups stratified according to the pre-DEXA FRAX®. The numbers represent the number of patients in each group. *, hence 42 DEXA scans could have been prevented.