Journal of Clinical Densitometry: Assessment & Management of Musculoskeletal Health, vol. ■, no. ■, 1–7, 2017

1094-6950/■:1–7/$36.00
http://dx.doi.org/10.1016/j.jocd.2017.05.010

Original Article

FRAX Score Can Be Used to Avoid Superfluous DXA Scans in Detecting Osteoporosis in Celiac Disease: Accuracy of the FRAX Score in Celiac Patients

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Abstract

The Fracture Risk Assessment (FRAX) tool has been developed to estimate patients' 10-yr probability of fracture, thus establishing which patients should undergo dual-energy X-ray Absorptiometry (DXA) scan. This study aimed to evaluate if the FRAX tool can replace or optimize the use of DXA scan in celiac disease (CD). We prospectively enrolled all CD patients aged over 40 yr diagnosed at our third-level unit. At time of CD diagnosis, all patients underwent FRAX score calculation for risk of major osteoporotic and hip fractures and DXA scan (used as *gold standard*) to assess the accuracy of the FRAX score. The FRAX score calculation was based on the following 10 variables: age (>40 yr), sex (M/F), body mass index, history of previous fracture (yes/no), parent fractured hip (yes/no), current smoking (yes/no), use of steroids (yes/no), rheumatoid arthritis (yes/no), secondary osteoporosis (yes/no), and alcohol ≥3 units/d (yes/no). DXA assessment was performed within 1 week from FRAX calculation. The FRAX score was dichotomized as normal or pathologic in accordance with the National Osteoporosis Guideline Group. A total of 160 CD patients were enrolled (M/F = 20/140; mean age 48.7 yr). A pathologic FRAX score was evident in 14 out of 160 patients (8.7%), whereas osteoporosis based on DXA scan was found in 10 patients (6%) ($\kappa = 0.6$); 3 patients with osteoporosis (1.9%) showed a 10-yr risk of major fracture >10% according to the National Osteoporosis Guideline Group criteria. With regard to diagnostic accuracy, the FRAX score showed sensitivity of 0%, specificity of 91%, positive predictive value of 0%, and negative predictive value of 94%. The prevalence of osteoporosis in adult CD appears to be quite low and only a small proportion of patients would require a DXA investigation. The FRAX score could be an effective tool to avoid useless DXA scans in CD patients in view of its high negative predictive value.

Key Words: Bone mineral density; celiac disease; DXA scan; FRAX score; osteoporosis.

Introduction

Celiac disease (CD) is the most common immune-mediated enteropathy in western countries, with a prevalence of about 1%, affecting genetically predisposed subjects (HLA DQ2/DQ8), who ingest gluten, a soluble protein from wheat, barley, and rye *(1)*.

As reported in a recent article by Ludvigsson et al *(2)*, classical CD is characterized by signs and symptoms of malabsorption, such as diarrhea, steatorrhea, and weight loss, whereas nonclassical CD presents with anemia, osteopenia/osteoporosis, dental enamel hypoplasia, and hypertransaminasemia.

In the last few years, evidence has shown how CD patients were at risk for other autoimmune or

Received 09/13/16; Revised 05/19/17; Accepted 05/19/17.
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immune-mediated diseases, neoplastic complications, and lower bone mineral density (BMD) *(3)*.

Low BMD, measured by using dual-energy X-ray absorptiometry (DXA), is a well-known risk factor for osteoporotic fractures *(4)*. In addition, the association between CD and low BMD is well established *(5,6)*, affecting up to 70% of patients with disease. Several studies conducted on a pediatric population suffering from CD have shown that low BMD responded to a gluten-free diet (GFD), with gradual and occasionally complete restoration to normal BMD levels *(7,8)*. Furthermore, BMD might also be restored in newly diagnosed adult CD patients after treatment with GFD *(9,10)*. Indeed, the improvement of BMD in CD subjects seems to be achieved mainly within the first year after starting GFD *(3,8,10–12)*. However, there was a vast inter- and intra-individual variability not only in the adherence (about 36%–96% of adult CD individuals are compliant *(13)*) but also in responding to GFD, which could be responsible for the failure in the restoration of BMD levels. From this point of view, it is well established that 97% of peak bone mass is gained in the first 2 decades of life, and full healing appears more complex in subsequent years *(14)*.

Recently, the Fracture Risk Assessment (FRAX) tool has been developed to estimate patients' 10-yr probability of fracture *(15)*. This tool has been widely used to decide which patients should undergo dual-energy X-ray Absorptiometry (DXA) scan and has helped determine appropriate therapy (e.g. bisphosphonates). On the other hand, some recent guidelines *(16–18)* recommend DXA scan for all patients at higher risk of osteoporosis, independently from the FRAX tool.

To the best of our knowledge, no data about the use of the FRAX tool in assessing the risk of bone fractures in CD are available in the current scientific literature.

The aims of this study were to evaluate if the FRAX tool can replace or optimize the use of DXA scan in CD, a well-known cause of secondary osteoporosis, and to establish the correct timing of DXA scan in the management of CD-related osteoporosis, avoiding superfluous X-ray examinations.

Materials and Methods

From September 2012 to June 2015 we prospectively and consecutively enrolled all CD patients aged over 40 yr diagnosed at our third-level University Center for adult CD and Food Intolerance at "Federico II" University in Naples, Italy. CD diagnosis was made in accordance with the current guidelines *(2)*. In these patients, first, serology was performed by using anti-endomysial antibodies (EMA) (present/absent) and a-tTG (U/mL) and then an esophagogastroduodenoscopy with duodenal biopsies was carried out. Diagnosis was confirmed when histology showed at least a Marsh grade ≥2 associated with both a-tTG IgA >7 U/mL and positive EMA. In accordance with the Oslo classification *(2)*, CD patients were divided in classical (diarrhea, steatorrhea, weight loss, growth failure, abdominal pain, bloating) and nonclassical (anemia, recurrent abortions, hepatic steatosis, dental enamel hypoplasia, hypertransaminasemia, recurrent aphthous stomatitis) groups and were presented separately. In accordance with current guidelines on osteoporosis *(16–18)*, all CD patients underwent DXA scan (used as *gold standard*) and FRAX score calculation for risk of major osteoporotic fracture and hip fracture at time of CD diagnosis to assess the accuracy of the FRAX score in diagnosing and predicting bone damage (osteoporosis/osteopenia) in CD. DXA assessment was performed within 1 week from FRAX calculation. All patients aged <40 yr were excluded from the study. Moreover, we excluded from the study patients who refused DXA scan. All patients gave their written consent.

FRAX Tool

The FRAX score *(16)*, assessed for the first time in the UK in 2008 and then validated in Canada in 2011, was constituted by the following 10 variables: age (>40 yr), sex (M/F), body mass index (BMI), history of previous fracture (yes/no), parent fractured hip (yes/no), current smoking (yes/no), use of steroids (yes/no), rheumatoid arthritis (yes/no), secondary osteoporosis (yes/no), and alcohol ≥3 units/d (yes/no). Thanks to age, BMI, and these abovementioned dichotomized risk factors, FRAX is able to calculate fracture probability. Femoral neck BMD can be optionally input to enhance fracture risk prediction. Fracture probability is computed, taking both the risk of fracture and the risk of death into account. The use of clinical risk factors in conjunction with BMD and age improves sensitivity of fracture prediction without adverse effects on specificity. Even if the performance of FRAX is enhanced by the use of BMD tests, it should be recognized that FRAX without BMD has a predictive value for fractures that is comparable to the use of BMD alone.

In particular, CD was considered a potential cause of secondary osteoporosis in all subjects. The FRAX score was dichotomized as normal or pathologic in accordance with the National Osteoporosis Guideline Group (NOGG) *(18)*. Fig. 1A and B shows the schemes used to assess the risk with and without using BMD. Data on personal and family history of fracture, rheumatoid arthritis, alcohol, and smoking habits were obtained during the anamnesis.

Osteoporosis and DXA Scan

Osteoporosis is a musculoskeletal disease characterized by decreased BMD and increased risk of fractures, and does not present any symptoms until a fracture occurs *(19)*. The assessment of BMD requires a DXA scan. DXA scans (Hologic QDR 1000, Hologic Inc., Waltham) were performed in accordance with the International Society for Clinical Densitometry-recommended National Health and Nutrition Examination Survey hands prone protocol *(20)*. The feet were divided by 15 cm for all scans. Standard or thick scan mode was machine-selected and dependent on