Addition of Alendronate to a Gluten Free Diet In Order to Increase Bone Mineral Density in Patients With Celiac Disease

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A. Study Purpose and Rationale

Celiac disease is a syndrome in which the ingestion of gluten, a protein contained in wheat, rye and barley products, causes morphological changes in the lining of the small intestine. The exact pathophysiologic processes responsible are not entirely clear at this time, but celiac disease is felt to be a result of an immune mediated process with some aspects consistent with a direct toxic effect of gluten.

It is important to note that not all individuals with celiac disease manifest the classic gastrointestinal symptoms of diarrhea, abdominal pain, bloating, steatorrhea and weight loss. Other possible clinical presentations include osteopenia/osteoporosis and iron deficiency or folate deficiency anemias. These processes result from the malabsorption seen with celiac disease.

Histologically, the epithelial lining of the small bowel in celiac patients reveal blunting of the microvilli with crypt hyperplasia. However, this finding is non-specific and a diagnosis of celiac disease is bases on clinical presentation, small bowel histology and the presence of anti-gliadin and anti-endomysial antibodies in the serum. The diagnosis is confirmed when the histologic changes seen in the small bowel are reversed when patients strictly follow a gluten free diet.

Low bone mineral density (BMD) has been shown to be a common complication of celiac disease. In one study, 70% of untreated and 42% of treated patients had a low BMD.[1] In a study of celiac patients presenting with the findings of hypocalcemia or skeletal pain, Shaker et al. found low BMD in all 8 patients in which it was measured.[2] While it has been postulated that the finding of low BMD in celiac patients is due to vitamin D deficiency, several studies document that the serum levels of vitamin D in these patients are normal in most cases.[2,3] Rather, the problem seems to be primarily a malabsorption of calcium. The serum calcium levels tend to be low normal with a secondary elevation in the level of parathyroid hormone, which stimulates osteoclasts to reabsorb bone. Markers of bone turnover such as bone specific alkaline phosphatase are also elevated in these patients.

Prospective studies that have evaluated changes in BMD in celiac patients maintained on a strict gluten free diet (GFD) have documented a statistically significant increase in the BMD over the course of 12 months.[1,3,4,5] However, while the increases in BMD have been statistically significant, the patients often remain in the osteopenic range (BMD between –1 and –2.5 standard deviations below the mean of healthy, young sex matched controls).[1]

Biphosphonate drugs have successfully been used both to treat and prevent osteoporosis.[6,7,8] These drugs work by inhibiting osteoclast activity. Alendronate (Fosamax) is a biphosphonate drug that can be administered orally. At a dosage of 5 mg. per day, it has been shown to be effective at preventing bone loss at the hip, lumbar spine and total body and to significantly increase BMD at the hip and lumbar spine. [7]

The purpose of this study is to evaluate the effectiveness of treating previously untreated patients with celiac disease with both a gluten free diet and fosamax in order to significantly increase their BMD's to a greater extent than a gluten free diet alone.

B. Study Design and Statistical Analysis

Study participants will be randomly assigned in an alternating fashion between the two arms of the study. The control arm will be placed on a gluten free diet and be provided with vitamin D and

calcium supplements. The patients in the experimental arm will be placed on a gluten free diet, be provided with calcium and vitamin D supplements and treated with alendronate, 5 mg. orally per day.

Based on data from previous studies, it was determined that an increase of 0.5 grams per squared centimeter of bone mineral density would be a significant finding. Given a standard deviation of 0.5g/cm, it was calculated that there would need to be 20 patients in each treatment arm to obtain a statistical power of 80%. The results will be analyzed using ANCOVA to determine statistical significance with an alpha value of 0.05.

C. Study Procedures

Each study patient will undergo dual X ray absoptiometry scan (DEXA) testing both at baseline and after one year to determine bone mineral density. BMD will be determined at the lumbar spine, trochanter, distal radius and total skeleton. Additionally, 5 cc of each patients serum will be drawn at baseline, 3, 6, 9 and 12 months. The serum samples will be analyzed for levels of both 25 OH Vitamin D and 1,25 OH Vitamin D, parathyroid hormone, total and ionized calcium, phosphate and bone specific alkaline phosphatase.

Prior to beginning the study, each participant will meet with a nutritionist. The nutritionist will provide education, menus, sources for gluten free food etc. for each participant. Each participant will be asked to keep a diet log for one week during each quarter of the study. Participants will be able to meet with the nutritionist on each quarterly visit.

Upon completion of the study, each participant will be interviewed to determine their compliance with the gluten free diet. Levels of anti-endomysial antibodies may also be checked at this time as thay should be in a normal range if the participant has strictly followed the diet.

D. Study Drugs

Both groups of participants will be maintained on calcium supplementation of 1 gm/day orally and 32,00 IU of Vitamin D per day orally. The experimental group will receive alendronate, 5 mg. orally on a daily basis. Alendronate (fosamax) is an appproved drug for the treatment and prevention of osteoporosis in post-menopausal women. It may be administered either orally or parentally. Dosages range from 1 mg. to 40 mg. daily. In a 1998 study, fosamax was found to have a safety and tolerability similar to that of placebo. [7] However, in another study it was found to have the following side effects in a dose dependent fashion: abdominal pain 6.6%, dyspepsia 3.6%, constipation 3.1%, diarrhea 3.1%, flatulence 2.6%, esophageal ulcer 1.55, abdominal distension 1.0%, dysphagia 1.0%. In addition there were mild, transient increase in liver function tests in a small fraction of patients.

Patients will need to be instructed to take fosamax in an upright position, at least 30 minutes before the ingestion of other food or drink. Fosamax should not be taken with calcium or dairy products as these will bind the drug and decrease absorption. Similarly, patients taking zantac should separate the two drugs, as zantac may raise blood levels of fosamax. Fosamax should be taken with 6-8 ounces of tap water.

E. Medical Devices

None

F. Study Questionnaires

None

G. Study Subjects

The study will include only adult patients over eighteen years of age of either sex. All study subjects will be untreated celiac patients diagnosed by clinical presentation, small bowel histology and serologic testing. Patients must have a BMD of less than 1 standard deviation below the mean relative to young, healthy sex matched controls. Patients with other diseases of bone or mineral metabolism, as well as subjects taking systemic glucocorticoids or high doses of thyroid hormone, will be excluded.

H. Recruitment of Subjects

Patients will be recruited by referral through the CPMC primary care network or through the department of gastroenterology. All primary care physicians will be contacted to determine if they feel the patient is suitable for the study and to ascertain whether the patient is willing to discuss the study with the research team.

I. Confidentiality

All patient information will be kept confidential.

J. Potential Conflict of Interest

None

K. Location of the Study

All study activities will be conducted at CPMC.

L. Potential Risks

The risks posed by the study drug at the dose of 5 mg. per day are minimal.

M. Potential Benefits

Patients stand to benefit by increasing their BMDs significantly greater than they might on a GFD alone.

N. Alternative Therapies

None

O. Compensation

None

P. Costs to Patients

None

Q. Minors as Research Subjects

None

R. Radiation or Radioactive Substances

None

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