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CELIAC DISEASE;

EFFECTIVENESS OF TREATING PREVIOUSLY UNTREATED PATIENTS WITH BOTH A GLUTEN FREE DIET AND BISPHOSPHONATE, GLUTEN FREE DIET ALONE.

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ABSTRACT… Objective: To evaluate effectiveness of treating previously untreated patients with celiac disease with both a gluten free diet and bisphosphonate in order to significantly increase their BMD's to a greater extent than a gluten free diet alone. **Patients and methods:** The study was conducted in National Institute of Child Health (NICH) Karachi to evaluate the effectiveness of treating previously untreated patients with celiac disease with a gluten free diet and bisphosphonate in terms of increase in bone mineral density in comparison to a gluten free diet alone over a period of three months (January 2013 – March 2013). The study includes 30 children patients below fifteen years of age either sex. All study subjects were untreated celiac patients diagnosed by clinical presentation, small bowel histology and serologic testing. On day dexa scan was done. Fifteen patients kept on Gluten Free Diet (GFD) and remaining 15 patients kept GFD plus tablet of bisphosphonate. After three months dexa scan was repeated. The patients with other disease of bone or mineral metabolism, as well as subjects taking systemic glucocorticoids or high doses of thyroid hormones, were excluded. **Results:** A total of 30 patients with celiac disease were included in this study. Out of 30 patients 18 (60%) were female and 12 (40%) male (M: F = 1:1.5). Thirty patients were divided in two equal groups (15 patients in each group). In group-I we gave gluten free diet and in group-II we gave gluten free diet and one tablet of bisphosphonate. Mean± SD of Bone Mineral Density (BMD) in group-I was 0.402± 0.081 gm/cm2 (range=0.234 – 0.503 gm/cm2), and in group-II was 0.543± 0.098 gm/cm2 (range= 0.402 – 0.743 gm/cm2), mean difference of bone mineral density was significant between two groups (P-value=0.0002). **Conclusions:** At three months DEXA scan showed a significant rise in BMD in group-II as compared to group-I

Key words: Celiac disease, bisphosphonate, gluten

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INTRODUCTION

Celiac disease (CD) is one of the common causes of malabsorption during infancy and childhood. The lesions of the small intestinal mucosa are secondary to a permanent intolerance to gluten. Osteoporosis, rickets, and osteomalacia can occur as a result of effective calcium absorption through the flattened mucosa sometimes associated with secondary lactose mal-absorption, increased endogenous calcium use, fecal loss and impaired vita-min D absorption. Adherence to a gluten-free diet (GFD) reverses the histological changes in the intestine and also the biochemical evidence of calcium malabsorption. It has long recognized that CD may be associated with disorders of the skeleton. Low bone mineral density (BMD) of all sites of skeleton has been shown to be a common complication of un-treated CD[1-3]. GFD does not always lead to improvement in BMD[4,5] and some authors have reported that 40% of treated patients with GFD have BMD below the normal mean[6].

A more recent study showed that a GFD promotes

a rapid increase of BMD to a sub-normal recovery of bone mineralization in children and adolescents with CD[7]. However, no data on the prevalence of osteopenia in patients with CD in children are currently available. 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[8,9,10,11]. However, while the increase 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 control)[8].

Bisphosphonate drugs have successfully been used both to treat and prevent osteoporosis[12-14].These drugs work by inhibiting osteoclast activity. Bisphosphonate drug that can be administrated 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[13]. There has been a growing recognition celiac disease is much more common than previously recognized and this has coincided with increasingly widespread use of serological testing.

PATIENTS AND METHODS

The study will include 30 children patients below fifteen years of age of either sex. All study subjects will be untreated celiac patients diagnosed by clinical presentation, small bowel histology and serologic testing. On day of enrolment Dexa scan was done. Fifteen patients kept on Gluten Free Diet (GFD) and remaining 15 patients kept GFD plus one tablet of Bisphosphonate. After three months dexa scan repeated. Patients with other disease of bone or mineral metabolism, as well as subjects taking systemic glucocorticoids or high doses of thyroid hormones, were excluded. Study participants were randomly assigned in an alternating fashion between the two groups of the study. The group-I was placed on a Gluten free diet. The patients in the group-II were placed on a gluten free diet & treated with bisphosphonate orally per day. Data was entered and analyzed by SPSS-12. Frequency and percentage was calculated for all qualitative variables including sex, age group and symptoms. While Mean± SD was computed for quantitative variables including age, Bone Mineral density (BMD), weight and height. Independent sample-test was used to compare the means of BMD, height and weight between two groups at 95% level of significance.

RESULTS

A total of 30 patients with celiac disease were included in this study. Out of 30 patients, 18 (60%) were female and 12 (40%) male (M: F = 1:1.5). table-I. Thirty patients were divided in two equal groups(15 patients in each group), in group-I we gave gluten free diet and in group-II we gave gluten free diet and one tablet of Bisphosphonate. Overall average age was 7.24± 2.24 years (Range =1.5 – 1.4 years). (Table-I) Difference of mean age was insignificant between two groups (P-value = 0.442), in group-I, mean± SD=6.6±4.3 years and in group-II, mean± SD=7.9±4.4 years. Mal-Absorption was the most common presenting symptom, was seen in 18 (60%) patients followed by Abdominal Distension in 17 (56.7%) patients, Height deficiency in 15 (50%) patients and Pallor in 8 (26.7%) patients Table-I. Mean± SD of Bone Mineral Density (BMD) in group-I was 0.402± 0.081 gm/cm2 (range=0.234 – 0.503 gm/cm2), and in group-II was 0.543± 0.098 gm/cm2 (range= 0.402 – 0.743 gm/cm2), mean difference of bone mineral density was significant between two groups (P-value=0.0002). Table-II. Mean± SD of weight in group-I was 14.1± 7.3 Kg (Range= 5.8 – 31 kg), and in group-II was 16.4± 7.4Kg (Range = 7.8 – 3.3 Kg), mean difference of weight was insignificant between two groups (P-value=0.388). Table-III. Mean± SD height in group-I was 100.7± 18 cm (Range = 78 – 131 cm), and in group-II was 108.9± 23.3 cm (Range 75-140 cm), mean difference of weight was insignificant between two groups (P-value=0.293) Table-III.

Parameter	Number of patients
Sex (M:F = 1:1.5) Male Female	 12 (40%) 18 (60%)
Age (Years)	**Mean ± SD = 7.24±4.4**
 1-5 6-10 11-15	**Range** = 1.5 - 14 15 (50%) 6 (20%) 9 (30%)
Symptoms Mal-Absorption Abdominal Distention Not Gaining Height Pallor	 18 (60%) 17 (56.7%) 15 (50%) 8 (26.7%)

Table-I. Demographic Variables (n = 30)

	Range gm/cm^2	Mean±SD gm/cm^2	p-value
Group-I n=15	0.234-0.503	0.402±0.081	0.0002
Group-II n=15	0.402-0.743	0.543±0.098	

Table-II. Comparison of bone mineral density between both groups (n=30)

Group-I = Patients with Gluten Free Diet
Group-II = Gluten Free Diet + Bisphosphonate Tab

Group	Height (cm) Mean ± SD (Range)	Weight (Kg) Mean ± SD (Range)
Group-I n=15	100.7±18 (78-131)	14.1±7.3 (5.8-31)
Group-II	108.9±23.3 (75-140)	16.4±7.4 (7.8-33)
P-value	0.293	0.388

Table-III. Comparison of weight and height between both groups (n=30)

Group-I = Patients with Gluten Free Diet
Group-II = Gluten Free Diet + Bisphosphonate Tab

DISCUSSION

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[8]. In a study of celiac patients presenting with the findings of hypocalcemia or skeletal pain, Shaker etal. Found low BMD in all 8 patients in which it was measured[9]. While it has been postulated that the finding of low BMD in celiac patients is due to vitamin D in these patients are normal in most case[9,10]. 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.

Mean± SD of bone Mineral Density (BMD) in group-I was 0.402± 0.081 gm/cm^2 (Range= 0.234 – 0.503 gm/cm^2), mean difference of bone mineral density was significantly high in group-II (P-value=0.0002). Bisphosphonate drugs have successfully been used both to treat and prevent osteoporosis[12,13,14]. These drugs work by inhibiting osteoclast activity. Bisphosphonate drug that can be administered orally. 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[13].

Malabsorption of both calcium and vitamin D progresses to osteopenia and osteoporosis[15]. Bone loss may also exist in celiac sprue in absence of gastrointestinal symptoms, therefore it is very important to perform screening for osteopenia or osteoporosis in all patients with CD[16]. On the other hand, screening of CD may be important in young individuals who have unexplained osteopenia or osteoporosis[17,18]. A study published in 2009 shown recently-diagnosed celiac patients following a gluten-free diet for five years. There was an increase in BMD, especially during the first year, which was maintained during the four following years. Normal levels of PTH and vitamin D were observed at the end of the follow-up[19]. Therefore, introduction of a gluten-free diet resulted in an increase in BMD with an improvement in biochemical parameters. In one year observation of alendronate therapy, the

mean BMD improvement of lumbar spine was 5.4% - 7.0% and the mean improvement of femoral neck was 2.6% - 4.5%[20]. Meanwhile in 2 years observation, the mean BMD improvement in lumbar spine was 7% and the mean improvement in femoral neck was 2%[20]. The specific indications for treatment for osteoporosis in patients with celiac disease are fragility fracture and low BMD with an increased risk of fracture[21,22]. The drugs used are the same as those of postmenopausal osteoporosis, with bisphosphonates being the gold standard[23]. Zoledronate IV given as a yearly dose may be a useful therapeutic option in these patients,[24] as the study by Black DM has shown its efficacy in reducing vertebral, nonvertebral and hip fractures, while parenteral administration would avoid absorption problems[25].

CONCLUSIONS

Both groups showed a decline in BMD in early months post transplantation. However the 3-month DEXA scan showed a significant rise in BMD in group-II as compared to group-I so we can say that Bisphosphonate appear to have a beneficial affect.

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