SHORT STATURE AND BONE MINERAL DENSITY IN CHILDREN WITH CELIAC DISEASE: A CROSS SECTIONAL STUDY

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Abstract:

Introduction: Children with celiac disease have long demonstrated an increased risk for fractures with reduced bone mineral density. Various studies have found hypocalcaemia, significantly decreased Vitamin D levels and increased Parathyroid hormones levels. Hence the study was planned to evaluate the occurrence of short stature and decreased bone mineral density and other blood parameters in children with celiac disease.

Materials and methods: 36 Children between the age group of 1-18 years with the diagnosis of celiac disease, Age and sex matched controls were enrolled. They were evaluated for Serum Calcium profile, Thyroid functions and Bone mineral density.

Results: Mean TSH level was significantly lower among the cases, while mean free T3 and free T4 levels were comparable among the two groups. The levels of serum calcium, serum phosphorous and ALP did not differ between cases and controls. The cases demonstrated a significantly decreased mean level of serum 25-OH cholecalciferol compared to the controls but PTH levels did not vary significantly between the cases and the controls and were within normal range. Mean Bone Mineral Density (Z score) among the Children with Celiac disease was -2.5 ± 0.22 with 42% (15 Patients) of them having Z score below -2SD i.e. low BMD.

Conclusion: Assessment of Vitamin D levels alone may not reflect the bone health in children with celiac disease. These children need to be evaluated with additional investigations like serum PTH levels and Bone mineral density, especially those children presenting with short stature at the time of diagnosis.

Introduction:

Celiac disease is a chronic small bowel enteropathy with many extra intestinal manifestations viz. short stature, anemia, fatigue, neurologic disorders, dental enamel defects, arthralgia, aphthous stomatitis etc. Atypical presentation occurs in 30-40% of patients diagnosed with celiac disease in India. Older children manifest commonly with extra intestinal symptoms. Children
with celiac disease have long demonstrated an increased risk for fractures with reduced bone mineral density.\textsuperscript{1,2} Though the pathology of bone disease is not completely understood, defects in calcium metabolism, compromised Vitamin D status with hyperparathyroidism have been postulated to cause a failure to acquire peak bone mass in growing children.\textsuperscript{2,3} Various studies have found hypocalcaemia, significantly decreased Vitamin D levels and increased Parathyroid hormones levels. They also have demonstrated increase in calcium and vitamin D levels with improvement in the hyper parathyroid states after treatment with GFD.\textsuperscript{1,3,4} More recently, role of pro-inflammatory mediators like TNF\textsubscript{a}, IFN\textsubscript{γ} have also been recognized to have been involved in the pathogenesis of bone loss.\textsuperscript{5} Celiac disease is associated with various other autoimmune phenomenon and comorbidities like hypothyroidism which contribute to the occurrence of short stature and disturbance in bone health. Hence the study was planned to evaluate the occurrence of short stature and decreased bone mineral density and other blood parameters in children with celiac disease. The current standard for measuring bone mineral density (BMD) is dual-energy X-ray absorptiometry (DXA), due to its availability, accuracy, ease of repetition, and patients’ low X-ray exposure. Using DXA analysis in pediatric population is complex, because of the bone mineral density changes during the process of growth and development. Children have not achieved their final bone mineral density; thus, every obtained result needs to be compared to the average value for the same sex and age (Z-score). Low BMD is when Z-score is lower than -2.0 SD.

Materials and methods:

The Cross Sectional Observational study was conducted in the Department of Pediatrics from 2015-2017 after institutional ethical committee clearance. Sample size was calculated on basis of previous study by Kavak et al.\textsuperscript{1} Thirty six children between the age group of 1-18 years with newly diagnosed celiac disease were enrolled for the study group. Age and sex matched children coming for routine vaccinations, minor afebrile illnesses and healthy siblings of the cases were enrolled for the control group. Informed written consent was taken from the parents of the children before enrollment. Children diagnosed with familial short stature, chronic skeletal disorders, children on chronic steroid therapy and those on Vitamin D supplementation were excluded from the study. Celiac disease was defined based on the guidelines by World Gastroenterology Organization - Guidelines for Celiac Disease 2012 for Children.\textsuperscript{6} Children with clinical symptoms or asymptomatic children with family history with positive serology* (IgA anti tTG antibodies) and biopsy findings (evidence of villous atrophy– Marsh staging 3) After enrollment, the details of the cases as well as controls were recorded in a pre-decided proforma. Venous blood from a peripheral vein was drawn after an overnight fasting and samples were collected in appropriate collection vials and the same were assessed as for Serum calcium, phosphorous, ALP, 25 OH Vitamin D and Parathyroid hormone as well Thyroid profile. The laboratory values were assessed according to standard reference values for age and sex.\textsuperscript{7,8} Bone Mineral Density was assessed only among the cases by performing dual-energy X-ray absorptiometry (DXA) analysis. BMD and Z-scores for the lumbar spine (LS) were recorded. Every obtained result was compared to the average value for the same sex and age (Z-score).

Statistical analysis was performed by the SPSS program for Windows, version 17.0. Continuous variables are presented as mean ± SD, and categorical variables are presented as absolute numbers and percentage. Data were checked for normality before statistical analysis. Normally distributed continuous variables were compared using the unpaired t test, whereas the Mann-Whitney U test was used for those variables that were not normally distributed. Categorical
variables were analyzed using either the chi square test or Fisher’s exact test. For within the group comparisons, spearman correlation was performed. For all statistical tests, a p value less than 0.05 was taken to indicate a significant difference.

Results:

Among the 36 cases included, youngest was 3 years old while the oldest was 16 years with a mean age of 7.72 ± 3.26 years. The control population was comparable in age distribution with a mean of 7.56 ± 3.18 years. Amongst cases 61.1% had short stature with height less than 3rd percentile, while only 5.6 % controls had short stature. Mean TSH level was significantly lower among the cases, while mean free T3 and free T4 levels were comparable among the two groups. The levels of serum calcium, serum phosphorous and ALP did not differ between cases and controls. The cases demonstrated a significantly decreased mean level of serum 25-OH cholecalciferol compared to the controls but PTH levels did not vary significantly between the cases and the controls and were within normal range. Mean Bone Mineral Density (Z score) among the Children with Celiac disease was -2.5 ± 0.22 with 42% (15 Patients) of them having Z score below -2SD i.e. low BMD.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>CASES</th>
<th>CONTROLS</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Age (Years)</td>
<td>7.72 ± 3.26</td>
<td>7.56 ± 3.18</td>
<td>0.827</td>
</tr>
<tr>
<td>Height &lt;3rd centile (%)</td>
<td>61.1%</td>
<td>5.6%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TSH (µU/ml)</td>
<td>2.42 ± 1.16</td>
<td>2.88 ± 0.89</td>
<td>0.029</td>
</tr>
<tr>
<td>Free T4 (µg/dl)</td>
<td>3.35 ± 10.37</td>
<td>1.2 ± 0.33</td>
<td>0.249</td>
</tr>
<tr>
<td>Free T3 (ng/dl)</td>
<td>4.2 ± 1.75</td>
<td>4.15 ± 0.96</td>
<td>0.681</td>
</tr>
<tr>
<td>Calcium (mg/dl)</td>
<td>9.19 ± 0.89</td>
<td>9.55 ± 0.87</td>
<td>0.109</td>
</tr>
<tr>
<td>S.Phosphorous (mg/dl)</td>
<td>4.51 ± 1.24</td>
<td>4.7 ± 1.01</td>
<td>0.677</td>
</tr>
<tr>
<td>ALP (U/L)</td>
<td>233.14 ± 88.97</td>
<td>232.78 ± 133.58</td>
<td>0.528</td>
</tr>
<tr>
<td>25-OH Vit D (ng/ml)</td>
<td>23.3 ± 16.28</td>
<td>29.2 ± 12.72</td>
<td>0.017</td>
</tr>
<tr>
<td>PTH (pg/ml)</td>
<td>80.25 ± 10.03</td>
<td>62.43 ± 10.21</td>
<td>0.765</td>
</tr>
<tr>
<td>Bone mineral density (Z score)</td>
<td>-2.5 ± 0.22</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Table 1: Parameters among cases and controls.
Discussion:

In our study, 22 cases (61.1%) had short stature with a height less than 3rd percentile while only 2 controls (5.6%) had short stature. Thus, height was significantly less among the cases with occurrence of short stature as one of the presenting feature at the time of diagnosis. There was a significant difference in TSH levels between cases and the controls with cases showing lower value of 2.42 ± 1.16 µU/ml as compared to 2.88 ± 0.89 µU/ml, but both were within normal range. 2 and 3 out of 36 cases did show decreased levels of free T4 and free T3 levels respectively which were not statistically significant. Similar results were also found in 2015 by Kalyoncu et al.9 assessing thyroid function in pediatric patients with celiac disease, who found no derangement of thyroid functions among the celiac patients at diagnosis. Such patients need further evaluation on follow up as celiac disease has been described to be associated with thyroid disorders more often than general population.10 Though the mean serum levels of calcium, phosphorous and ALP among the cases were normal, mean 25-OH Vitamin D levels were significantly lower among the cases with a mean of 23.3 ± 16.28 ng/ml as compared to controls with a mean of 29.2 ± 12.72 ng/ml (p value 0.017). 27.8% of the cases had increased parathyroid levels and 30.6% had hypocalcaemia, none of them had features of vitamin D deficiency clinically except for short stature. Mean Bone Mineral Density (Z score) among the Children with Celiac disease was -2.5 ± 0.22. Among the 22 cases with short stature, none had decreased TSH or Vitamin D3 levels, one child (4.5%) had decreased fT3 levels, 8 children (36.4%) had decreased calcium levels, 7 children (31.8%) had decreased phosphorous levels and 3 (13.6%) had increased phosphorous levels, one child (4.5%) had increased ALP levels and also 7 children (31.8%) had increased PTH levels, 13 (36%) had low BMD. Among the 15 cases with low BMD, no child (0%) had decreased fT3 levels or increased ALP levels, 6 children (40%) had decreased calcium levels, 5 children (33.3%) had decreased phosphorous levels and 8( 53%) had increased phosphorous levels, and also 6 children (40%) had increased PTH levels. It is well explained that increased parathyroid can be associated with bone loss. In 1999, Selby et al11 found reduced bone mineral density associated with secondary hyperparathyroidism without vitamin D deficiency in celiac patients. Also, in 2000, Valdimarsson et al.12 demonstrated lower BMD after three years follow up in patients with initial secondary hyperparathyroidism. Kavak et al.13 in 2003 studying bone mineral density among celiac patients, demonstrated similar results with 17.6% of the patients showing hypocalcaemia and 29.4% of patients with elevated parathyroid hormone levels. While in 2008 Zanchi et al.3 reported significantly decreased 25-OH vitamin D levels and increased PTH levels among celiacs, later in 2012 Villanueva et al.4 demonstrated results like that of our study with no difference in vitamin D levels between celiac patients and healthy children.

Conclusion:

Assessment of Vitamin D levels alone may not reflect the bone health in children with celiac disease. These children need to be evaluated with additional investigations like serum PTH levels and Bone mineral density, especially those children presenting with short stature at the time of diagnosis.

Limitations:

Effect of GFD on the study parameters could not be done as it was a cross sectional study and follow up was not done. Only central BMD at Lumbar spine was assessed
Conflict of interests: None

Finding: None

References: