Markers of bone turnover in prepubertal children with celiac disease

Active celiac disease (CD) is known to predispose patients to disturbances in bone metabolism. However, little information is available on biochemical bone turnover markers in prepubertal celiac children treated with gluten-free diet (GFD).

We investigated 5 children with celiac disease (age range 1.5-8 years; 3 girls). Celiac disease was confirmed by villous atrophy, crypt hyperplasia, increased intraepithelial lymphocyte counts on duodenal biopsies, and positive antiendomysial antibodies on gluten diet. Bone turnover markers were tested after patients were on GFD for 0.5-3.5 years. The markers (25-hydroxycalciferol [25OH-D vitamin], calcium and phosphate) were measured 3 times on GFD, over 1.5 years (0, 9, 18 months). Compliance with the diet was ascertained by negative results of testing for antiendomysial antibodies. Calcium and 25OH-D supplements were not given or recommended. Body mass index (BMI) was calculated from anthropometric data. The reference group consisted of 25 healthy children (range 2-8 years; 15 girls) sent to our laboratory for other tests. None of the patients or volunteers had other diseases or had taken drugs known to influence bone metabolism. Control subjects were volunteers who had changes in the pattern of bone turnover markers. Further studies of these patients are needed to assess their predisposition to metabolic bone disorders.

Venous blood samples were collected after an overnight fast and centrifuged, and serum samples were frozen at –20 °C until analysis. Serum OC (osteocalcin) and CTX (C-terminal telopeptide of type 1 collagen) were determined by immunoenzymatic ELISA assays (Nordic Bioscience Diagnostics A/S, Denmark), BALP (bone alkaline phosphatase) by the Alphase-B kit (Metra Biosystems, USA), 25OH-D vitamin by the kit from Biomedica (Austria). Calcium and phosphate were estimated with a Cobas Integra analyzer (Roche, Switzerland).

In healthy children the median values (ranges) for CTX were 2.02 µg/L (1.36-2.43), for OC 113.8 µg/L (75.4–135.0), for BALP 101.9 U/L (55.1-140.7) and for 25OH-D vitamin 30 µg/L (14-54). Serum values of these markers for individuals patients are shown in the Table. Lower median values of CTX were obtained in 4 tested patients as compared to the controls. In all patients median OC concentration was lower than in healthy children, whereas low median BALP activity was found in only one patient. In most patients values of bone turnover markers were similar to those in the controls. One patient had markedly low values of all three bone turnover markers.

Practico et al observed in prepubertal children lower values of OC before the start of a gluten-free diet, whilst on GFD they obtained a progressive return to normal of the serum levels. In our study also we observed normal values of OC concentration in most patients on GFD. Barera et al observed in young children during GFD a gradual and significant increase in BALP activity. On the contrary, the concentration of the resorption marker — urinary NTX (N-terminal telopeptide of type 1 collagen) — was significantly higher than in controls and was not affected by treatment. We found the same trend for BALP, whilst for CTX, which like NTX is a resorption marker, an opposite trend was noted. Lower CTX levels may suggest disturbances in the bone resorption process.

Our observations show normalization of bone resorption and formation markers in serum in most patients with celiac disease on GFD. However, some cases had changes in the pattern of bone turnover markers. Further studies of these patients are needed to assess their predisposition to metabolic bone disorders.

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**Table: Clinical and biochemical data of patients with celiac disease**

<table>
<thead>
<tr>
<th>Sex</th>
<th>Age at diagnosis (y)</th>
<th>BMI (Kg/m²)</th>
<th>OC (µg/L)</th>
<th>CTX (µg/L)</th>
<th>BALP (U/L)</th>
<th>25OH-D vitamin (µg/L)</th>
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</thead>
<tbody>
<tr>
<td>F</td>
<td>1.0</td>
<td>15.3; 14.8; 14.7</td>
<td>63.5; 92.3; 120.7</td>
<td>105.9; 88.2; 118.5</td>
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</tr>
<tr>
<td>M</td>
<td>1.5</td>
<td>13.9; 12.8; 13.3</td>
<td>50.8; 77.3; 69.2</td>
<td>62.2; 104.0; 137.8</td>
<td>54.8; 25.2; 40.0</td>
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</tr>
<tr>
<td>M</td>
<td>1.5</td>
<td>16.2; 15.9; 16.2</td>
<td>71.8; 38.5; 22.5</td>
<td>52.6; 55.1; 70.3</td>
<td>24.7; 24.2; 23.8</td>
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<tr>
<td>F</td>
<td>3.0</td>
<td>12.7; 13.0; 12.9</td>
<td>99.6; 109.5; 91.8</td>
<td>164.9; 105.4; 117.8</td>
<td>20.3; 27.9; 24.1</td>
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</tr>
<tr>
<td>F</td>
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<td>13.2; 13.6; 13.4</td>
<td>102.5; 104.0; 103.3</td>
<td>99.8; 109.6; 104.7</td>
<td>20.3; 23.3; 26.6</td>
<td></td>
</tr>
</tbody>
</table>

Data expressed are values obtained at 0, 9 and 18 months on GFD.

References


Letters
One month after surgery, the patient was noted to have multiple papules of 1 mm to 4 mm diameter; a few of those coalesced to form plaques, all round the neck, axilla and groin. The skin was lax and redundant in the neck and its surface was rough and plebby. Ocular fundus examination revealed angiod streaks and multiple peripapillary mottling in both eyes. Skin biopsy from the involved area in the neck showed focally thickened epidermis, fragmented elastic fibers in the reticular dermis along with collection of histiocytes, and giant cells in the dermis and calcification. Repeat endoscopy showed normal gastric mucosa. Histology of the splenectomy specimen revealed fragmented elastic fibers in the large-sized muscular arteries, with calcification. Ultrasonography and CT scan of the abdomen showed diffusely scattered calcific specks in the cortex and medulla of both the kidneys, suggesting nephrocalcinosis. Biochemical investigations including serum calcium, serum phosphate, serum proteins, renal function tests, and 24-hour urinary excretion of sodium, potassium, calcium, inorganic phosphate, creatinine and proteins were within normal limits. Urinary ammonium chloride load test for acid excretion and arterial pH were also normal.

In a review of 200 patients with PXE collected from the literature, GI bleeding was reported in 13% of patients.2 It is usually gastric in origin, and recurrent.2-5 Our patient had the first episode of UGI bleeding at the age of 4 years, which is the youngest age at onset of bleeding reported in patients with PXE. GI bleeding is thought to result from degeneration of the elastic fibers in the arterial wall, which leads to aneurysmal dilatation and subsequent rupture of the vessels.2 The inability of arterioles to retract also increases chances of hemorrhage from unrelated causes such as peptic ulcer disease or other mucosal injuries.2,3,4 The characteristic endoscopic findings include distinctive yellow cobblestone appearance or nodular raised submucosal lesions similar to xanthoma-like lesions of the skin as seen in this condition.5 Our patient also had evidence of nephrocalcinosis. The renal calcification in PXE is generally limited to the cortico-medullary junction. To the best of our knowledge, diffuse renal calcification has not been described earlier in patients with PXE. It is possible that these calcific specks represent areas of vascular degeneration with calcification in the renal parenchyma.

There is no specific treatment for PXE. Anti-secretory drugs and vasoconstricting agents are frequently unsuccessful in controlling bleeding.2,5 Angiographic embolization of involved vessels has been used with variable results.2,3,4 Partial gastrectomy, total gastrectomy, oversewing of the bleeding site and gastric devascularization are the usual surgical options in patients who have recurrent UGI bleeding. 2-5 Gastric devascularization done in our patient with a presumptive diagnosis of portal hypertension incidentally is also a mode of treatment for gastric bleeding in patients with PXE.

Pseudoxanthoma elasticum: a rare cause of recurrent gastrointestinal bleeding in a child

Pseudoxanthoma elasticum (PXE) is an inherited connective tissue disorder characterized histologically by elastorrhexis affecting the elastic tissues in the dermis, blood vessels and Bruch’s membrane of the eye. Diagnosis is based on the presence of classical skin lesions, angiod streaks, and demonstration of characteristic findings on skin biopsy.1 Patients with PXE are known to present with recurrent upper gastrointestinal (UGI) bleeding.2-5

An 11-year-old boy presented with recurrent painless UGI bleeding (hematemesis and melena) since the age of 4 years. None of the bleeding episodes was associated with ingestion of drugs, jaundice or encephalopathy. Repeated UGI endoscopies, abdominal ultrasonography, barium meal follow-through and liver biopsy had not revealed any diagnosis. During the present admission, he had severe pallor and splenomegaly. On UGI endoscopy, there were no esophageal varices but there was a pool of blood in the gastric fundus. In addition, the gastric folds appeared prominent in the gastric fundus and an active ooze was seen. Ultrasonography showed normal liver and portal vein; the splenic vein could not be visualized.

Despite blood transfusion and gastric tamponade with a Sengstaken-Blakemore tube, GI bleeding continued. With a provisional diagnosis of portal hypertension due to sphenic vein thrombosis, gastric devascularization and splenectomy were done.

References

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