Periostin and sclerostin levels in juvenile Paget’s disease

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Case report

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Introduction

Juvenile Paget’s disease (JPD) is a rare, autosomal recessive disorder featuring markedly increased serum alkaline phosphatase activity, indicative of greatly accelerated bone turnover throughout the skeleton (1). Patients present early skeletal implication, including malformations and low-energy fractures, and later non-skeletal manifestations, including retinopathy, hearing loss, vascular calcification and internal carotid artery aneurysms formation (1-3). Most patients have homozygous loss-of-function mutations of the TNFRSF11B gene, resulting in deficient or non-functioning osteoprotegerin (2, 4). To the best of our knowledge, JPD due to homozygosity for the TNFRSF11B “Balkan mutation” (966_969delTGACinsCTT), resulting in non-functioning osteoprotegerin, has been described in only five patients to date (5).

Periostin, a secreted extracellular matrix protein, is expressed in collagen rich connective tissues and interacts with several cell surface integrins, providing signals for tissue development and remodeling (6). Sclerostin, produced almost exclusively by the osteocytes, is a negative regulator of the canonical Wingless (Wnt)/β-catenin signaling, thus inhibiting osteoblastic bone formation (7). It has been supported that periostin could regulate sclerostin expression and possibly Wnt/β-catenin regulated genes, including that of osteoprotegerin, in osteocytes, through interacting with integrin receptors and canonical Wnt/β-catenin pathway (8). However, periostin and sclerostin levels have not been evaluated in JPD, a disease largely owing to osteoprotegerin insufficiency.

The main aim of this study was to evaluate circulating periostin and sclerostin levels in two adult patients with mild JPD (due to “Balkan” mutation).

Patients and methods

Patient #1 is a previously described 35-year woman with TNFRSF11B “Balkan mutation” (966_969delTGACinsCTT) (5, 9). Patient #2 is a 33-year man, recently confirmed to be homozygous for the same mutation, but not previously described. Both patients had received many courses of calcitonin and bisphosphonates in the past with moderate results, especially in patient #1. For the needs of this study, we recruited as controls 10 (5 women) apparently healthy individuals, matched (1:5) to JPD patients for gender, age and body mass index. Sclerostin levels were similar between JPD patients and controls. Periostin levels were about 2.5 times higher in JPD patients. Periostin and sclerostin levels were negatively correlated (rs = -0.63; p=0.03).

In conclusion, a trend towards higher periostin levels was observed in JPD patients, whereas sclerostin levels were similar to controls.

KEY WORDS: CTX; juvenile Paget’s disease; PINP; periostin; sclerostin.
physiologically different from JPD. Moreover, periostin has been positively associated with fracture risk, but not with bone mineral density in postmenopausal osteoporosis (11, 13). Despite the trend towards higher periostin levels and the definitely higher risk of fracture in JPD, the design of this study cannot support that periostin levels could determine fracture risk in JPD, a speculation, however, warranting further investigation.

As for sclerostin, we had hypothesized that JPD patients would have lower sclerostin levels, a condition permissive for Wnt/β-catenin pathway to upregulate osteoprotegerin; however, no statistical difference was observed between patients and controls. Some Authors reported similar (14), while others higher (15, 16) sclerostin levels in patients with Paget’s disease of bone compared with controls. This discrepancy might be partly attributed to population differences (gender and/or age and/or BMI differences between patients and controls in the same study or between different studies).

Since sclerostin was shown different between patients with monostotic and polyostotic Paget’s disease of bone (15), different rates of monostotic and polyostotic disease in different studies might have also affected mean sclerostin levels. In any case, Paget’s disease of bone and JPD are different diseases and observations in Paget’s disease of bone may not apply to JPD.

Certain limitation of this study is its small sample size, which may have resulted in false negative results; however, the rarity of the disease and the specific mutation renders the assembly of larger groups a difficult task. Setting a multinational database of JPD patients may be of importance for more efficient studying and management of the disease. Strength of the study is the fact that bone turnover was similar between JPD patients and controls, meaning that periostin and sclerostin were evaluated at a relatively inactive period of the disease.

In conclusion, a trend towards higher periostin levels was observed in JPD patients, whereas sclerostin levels were similar to controls. Further studies with larger samples and different design are needed to validate these results and elucidate potential clinical implications, including the utility of periostin as a risk factor of fractures.

Funding

No source of grant or fellowship supported this study.

Table 1 - Comparative data between patients with juvenile Paget’s disease and controls.

<table>
<thead>
<tr>
<th></th>
<th>Control group</th>
<th>JPD patients</th>
<th>p-value *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients / Women (N)</td>
<td>10 / 5</td>
<td>2 / 1</td>
<td>1.00</td>
</tr>
<tr>
<td>Age (years)</td>
<td>34.0 ± 1.2</td>
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<td>BMI (kg/m²)</td>
<td>25.6 ± 1.0</td>
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<td>PINP (ng/ml)</td>
<td>45.8 ± 4.7</td>
<td>44.2 ± 2.7</td>
<td>1.00</td>
</tr>
<tr>
<td>CTX (ng/ml)</td>
<td>0.40 ± 0.05</td>
<td>0.37 ± 0.16</td>
<td>0.83</td>
</tr>
<tr>
<td>Sclerostin (pmol/l)</td>
<td>53.1 ± 9.4</td>
<td>36.6 ± 10.3</td>
<td>0.52</td>
</tr>
<tr>
<td>Periostin (ng/ml)</td>
<td>487 ± 125</td>
<td>1212 ± 289</td>
<td>0.09</td>
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Data are presented as mean ± standard error of the mean (SEM). Comparisons between JPD patients and controls were performed with nonparametric tests: Mann-Whitney test for continuous and Fischer exact test for categorical variables. Abbreviations: BMI, body mass index; CTX, C-terminal telopeptide of type I collagen; PINP, procollagen type I N-terminal propeptide.

Results

Total alkaline phosphatase, considered an index of the disease activity, was 145 U/l and 108 U/l (reference range 25-130 U/l) in patient #1 and #2, respectively. Comparative data between JPD patients and controls are presented in Table 1. PINP and CTX were similar between JPD patients and controls. Sclerostin levels were similar between JPD patients and controls. Periostin levels were about 2.5 times higher in JPD patients and/or age and/or BMI differences between patients and controls may have resulted in false negative results; however, the rarity of the disease and the specific mutation renders the assembly of larger groups a difficult task. Setting a multinational database of JPD patients may be of importance for more efficient studying and management of the disease. Strength of the study is the fact that bone turnover was similar between JPD patients and controls, meaning that periostin and sclerostin were evaluated at a relatively inactive period of the disease.

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Conflict of interest
All Authors have no conflicts of interest.

References