Non-enzymatic collagen cross-links, pentosidine, predicts vertebral fractures

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Introduction: Osteoporosis is characterized by compromised bone strength, increased susceptibility to fractures that impair patient’s quality of life. We have revealed that collagen enzymatic and non-enzymatic cross-links play an important role in the bone strength (1-4) and proper biological function of bone (5-7). Cross-linking of collagen involves two different mechanisms, one a precise lysyl oxidase (LOX) controlled cross-linking, which is assumed to improve the material properties, and the other non-enzymatic cross-linking (Advanced glycation end products: AGEs, pentosidine), which is thought to deteriorate the mechanical properties of bone. However, there are no available data on the relationship between susceptibility to bone fractures and AGEs cross-links of collagen in clinical samples. Thus, we investigated the association between collagens and fracture risk in post-menopausal women.

Materials and Methods: The data of the present study were a subset of Nagano cohort study (8) and consisted of peri- or post-menopausal women (a total of 432 subjects) at baseline and post-menopausal osteoporotic women who had not received treatment (other than dietary instruction) for osteoporosis during the observation period. Markers of bone collagen metabolites were measured at entry. Thoracic and lumbar radiographs were taken at entry and followed at 1 to 2-year intervals or indicate symptoms such as back pain. Axial BMD (lumbar BMD) was measured at entry and also followed at the same intervals. Two markers of bone collagen metabolites were measured in spot urine samples. Urinary N-terminal telopeptide of type I collagen (NTX) was measured by an ELISA kit (Osteomark Ostex Co., Princeton, NJ, USA). Urinary levels of pentosidine were measured by our established HPLC (1). Statistical Analyses: Since the NTX and pentosidine levels in urine samples distributed asymmetrically, natural log transformed values of these parameters were used. We also report the number and proportion of patients for categorical data and count of incident vertebral fractures. In the primary analysis, we used the length of time from participation in our study to the first vertebral fracture as endpoint and analyzed by time-to-event methods. Outcome comparisons are presented as hazard ratios, 95% confidence intervals (CI) and p-values from Cox’s proportional hazard models. Therefore, among urinary level of pentosidine is a significant risk for future vertebral fracture.

Discussion: We found that urinary excretion of pentosidine is associated with future vertebral fracture risk independent of other traditional fracture risks such as pre-existing fracture, BMD or age. This finding may provide new insight in the research on bone strength.

References: (1) Saito et al., Anal Biochem, 253:23-32, 1997
(2) Saito et al., Osteoporos Int, 17:986-995, 2006
(3) Saito et al., Osteoporos Int, 17:1514-1523, 2006
(4) Saito et al., Calcif Tissue Int, 79:69-77, 2001
(5) Saito et al., Bone Miner, 16:169-175, 2003
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(8) Shiraki et al., J Bone Miner Metab 24:219-225, 2006

Table 1. Incident vertebral fracture rates in quartiles of NTX and pentosidine in urine

<table>
<thead>
<tr>
<th>Quartile</th>
<th>Actual rate of NTX (ng/mg Cr)</th>
<th>HR for NTX (fracture/years)</th>
<th>Actual rate of pentosidine (ng/mg Cr)</th>
<th>HR for pentosidine (fracture/years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q1</td>
<td>456.82</td>
<td>1.00</td>
<td>45.36</td>
<td>1.00</td>
</tr>
<tr>
<td>Q2</td>
<td>475.45</td>
<td>1.11</td>
<td>41.78</td>
<td>0.94</td>
</tr>
<tr>
<td>Q3</td>
<td>456.32</td>
<td>1.22</td>
<td>37.50</td>
<td>0.85</td>
</tr>
<tr>
<td>Q4</td>
<td>502.02</td>
<td>1.33</td>
<td>43.70</td>
<td>0.69</td>
</tr>
</tbody>
</table>

Incident fracture rates (HR) for individual quartiles of NTX and pentosidine were calculated and compared test was conducted by log rank test.

Fig. 1. Cumulative incident vertebral fracture rates for individual quartiles of urinary pentosidine level.

Cumulative incident vertebral fracture rates for individual quartiles of urinary pentosidine level. The group with highest quartile of urinary level of pentosidine showed significantly higher and faster occurrence of incident vertebral fractures than the other quartiles.

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