Severe osteoporosis with multiple vertebral fractures after gender reassignment therapy – is it male or female osteoporosis?

<table>
<thead>
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<td>DGYE-2010-0023.R1</td>
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<td>Case Report</td>
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<td>Date Submitted by the Author:</td>
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<tr>
<td>Complete List of Authors:</td>
<td>Fischer, Eva-Maria; St.Vincent Hospital, Medical Dep.II Patsch, Janina; St.Vincent Hospital, Medical Dep.II Muschitz, Christian; St.Vincent Hospital, Medical Dep.II Becker, Stephan; Orthopedic Hospital Speising Resch, Heinrich; St.Vincent Hospital, Medical Dep.II</td>
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Case Report

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Eva-Maria Fischer¹, Janina Patsch¹, Christian Muschitz¹, Stephan Becker² and Heinrich Resch¹

¹St. Vincent Hospital, Medical Department II, Vienna Austria
²Orthopedic Hospital Speising, Vienna Austria

Short running title: Osteoporosis after gender reassignment therapy

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Concerning the anamnesis the patient has a history of a gastrointestinal disorder. Since youth she suffers from alternating episodes of diarrhoea and constipation. 2006 an unspecified colitis was diagnosed which was treated with mesalazine. Recent investigations showed no evidence of an inflammatory bowel disease or celiac disease, mostly indicating an irritable bowel syndrome.

She is non-smoking, vegan and does not consume products containing lactose. The patient’s parents were both suffering from osteoporosis.

The medication was 1200mg Calcium, 800 IU Vitamin D and 200 IU Calcitonin daily.

The patient’s fracture history, the different compounds of HRT (hormone replacement therapy) and the blood estradiol levels are shown in Table 1. The first vertebral fractures of L2 and L5 occurred in 1994 after a bicycle accident. However, 9 years after initial HRT she had the first atraumatic fractures. From 2004 till 2006 she sustained fragility fractures of the right radius, ribs VIII, IX, X, Th6, Th12, L3 and cover plate impressions of Th9, Th11 and L1. Because of severe clinical symptoms a kyphoplasty of Th11, Th12 and L1 was performed which led to a relief of the lumbar pain.

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**Acknowledgments:** The BMDD parameter measurements were kindly provided by the Ludwig Boltzmann Institute of Osteology at the Hanusch Hospital of WGKK and AUVA Trauma Centre Meidling, 4th Medical Department, Hanusch Hospital, Vienna, Austria

**References**


4. Reginster JY, Neuprez A, Bruyère O. Ibandronate in profile: drug characteristics
and clinical efficacy. Expert Opinion on Drug Metabolism & Toxicology 2008;4(7):941-951


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References


Table 1 Fracture history in relation to HRT and estradiol levels

<table>
<thead>
<tr>
<th>Date</th>
<th>Hormone Therapy</th>
<th>Fractures</th>
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<th>Testosterone (ng/ml)</th>
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<tr>
<td>1985-1988</td>
<td>norethisterone</td>
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<td>1989-1992</td>
<td>androcur 2’t g /Trisequenz forte</td>
<td>1,044</td>
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<td>1992-1993</td>
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<tr>
<td></td>
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<tr>
<td></td>
<td>547</td>
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<td>1993</td>
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<td>estral 2mg/1mg</td>
<td>L2, L5</td>
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<td>2001-2002</td>
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<td>269</td>
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<tr>
<td>2002-2007</td>
<td>desmin 20/remifemin</td>
<td>radius right, ribs 6,9,10 right,</td>
<td>23</td>
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<tr>
<td></td>
<td></td>
<td>Th6, Th12, L3, cover plate impression</td>
<td>&lt;3.0</td>
<td>0.54</td>
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<tr>
<td></td>
<td></td>
<td>Th9, Th11, L1, kyphoplasty Th11, Th12, L1</td>
<td>&lt;3.0</td>
<td>0.54</td>
</tr>
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</table>
Figure 1 X-ray of the lumbar spine
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Apart the cross-sex hormone replacement therapy for the gender reassignment the patient has additive risks that are related to osteoporosis like the positive family history, her lactose-free lifestyle since 2003 and an unspecific colitis. However, our investigations including colonoscopy with biopsies did not show any evidence of an inflammatory bowel disease or celiac disease mostly indicating an irritable bowel syndrome which has no causal relation to osteoporosis.

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References


Table 2 Analysis of Biochemical Markers, Bone Structure and BMDD

<table>
<thead>
<tr>
<th>Blood Analysis</th>
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<tbody>
<tr>
<td>Calcium</td>
<td>2.21 mmol/l</td>
<td>(2.10-2.58)</td>
</tr>
<tr>
<td>Phosphate</td>
<td>0.92 mmol/l</td>
<td>(0.60-1.55)</td>
</tr>
<tr>
<td>Parathormone/serum</td>
<td>43.6 pg/ml</td>
<td>(11.1-79.5)</td>
</tr>
<tr>
<td>Vitamin D (25-OH)</td>
<td>29.26 ng/ml</td>
<td>(19-58)</td>
</tr>
<tr>
<td>Crosslaps/serum (CTx)</td>
<td>0.193 ng/ml</td>
<td>(&lt;0.6)</td>
</tr>
<tr>
<td>Procollagen I (PINP)</td>
<td>26.9 µg/l</td>
<td>(16-74)</td>
</tr>
<tr>
<td>Alkaline Phosphatase</td>
<td>93 U/l</td>
<td>(35-104)</td>
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<table>
<thead>
<tr>
<th>Bone structure analysis (µ-CT)</th>
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<tbody>
<tr>
<td>BV/TV</td>
</tr>
<tr>
<td>Conn.Dens. ([1/mm3])</td>
</tr>
<tr>
<td>SMI [1]</td>
</tr>
<tr>
<td>Tb.N [1/mm]</td>
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<td>Tb.Th [mm]</td>
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<td>Tb.Sp. [mm]</td>
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<table>
<thead>
<tr>
<th>BMDD measured by qBEI</th>
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<tr>
<td>BMDD parameters</td>
</tr>
<tr>
<td>Ca_MEAN [wt% Ca]</td>
</tr>
<tr>
<td>Ca_PEAK [wt% Ca]</td>
</tr>
<tr>
<td>Ca_WIDTH [Awt% Ca]</td>
</tr>
<tr>
<td>Ca_LOW [%]</td>
</tr>
<tr>
<td>Ca_HIGH [%]</td>
</tr>
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</table>

Reference data given in mean (SD)

Abbreviations:
- Ca\_MEAN = weight mean calcium content of bone obtained from the integrated area under the BMDD curve
- Ca\_PEAK = most frequent calcium content
- Ca\_WIDTH = full width at one-half maximum of BMDD peak, indicating the heterogeneity of mineralization
- Ca\_LOW = amount of bone with less mineralization density than 17.68 weight% calcium as an indicator of newly formed bone
- Ca\_HIGH = amount of bone with more mineralization density than 25.30 weight% calcium as an indicator of newly formed bone
- BMDD = Bone Mineralization Density Distribution
- qBEI = quantitative backscattered electron imaging
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Manuscript number: DGYE-2010-0023

was submitted for publication in:

JOURNAL OF GYNECOLOGICAL ENDOCRINOLOGY

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