The neuroendocrine axis and the skeleton

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Pituitary-bone axis

Endocrine causes of osteoporosis: focus on the pituitary-bone axis

Agenda

- Physiology
- Hypopituitarism
  - GH deficiency
  - GC replacement therapy
- Hyperpituitarism
  - GH excess (acromegaly)
  - PRL excess (prolactinoma)
  - ACTH excess (Cushing’s disease)
- Exogenous Cushing’s syndrome
Endocrine causes of osteoporosis: focus on the pituitary-bone axis

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**GH-IGF-I and bone/1**

*Overview*

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**GH-IGF-I and bone/2**

*IGF-I as mediator of GH and PTH effects on osteoblasts*
Prolactin effects on bone remodelling

Direct effects on osteoblasts

Seriwatanachai et al., Bone 2008
Seriwatanachai et al., J Cell Biochem 2009

Glucocorticoids and bone/1

Overview

Seriwatanachai et al., Bone 2008
Seriwatanachai et al., J Cell Biochem 2009

Glucocorticoids and bone/2

Effects on PTH secretion

Bonadonna et al., Eur J Endocrinol 2005
Neuroendocrine diseases and bone

**Agenda**

- Physiology
- **Hypopituitarism**
  - GH deficiency
  - GC replacement therapy
- **Hyperpituitarism**
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  - ACTH excess (Cushing’s disease)
- **Exogenous Cushing’s syndrome**
Adult hypopituitarism/1
Epidemiology
- Non-functioning pituitary macro-adenoma
- Parasellar tumors
- Neurosurgery for pituitary and hypothalamic tumors
- History of cranial irradiation
- Empty sella syndrome
- Post-partum pituitary necrosis (Sheehan’s Syndrome)
- Lymphocytic hypophysitis
- Infiltrative/granulomatous diseases
- History of traumatic brain injury
- History of subarachnoid hemorrhage,

Adult hypopituitarism/2
Clinical features
- Visceral obesity
- Insulin-resistance
- Dyslipidemia
- Impaired quality of life
- Osteoporosis/Osteopenia and fragility fractures

Adult hypopituitarism/3
GHD and skeletal health

GHD has a central role in determining bone loss in hypopituitarism patients

[Wuster et al., J Bone Miner Res. 2003]
Adult hypopituitarism/4

GHD and bone turnover

Colao et al., JCE&M 1999

Adult hypopituitarism/5

GHD and BMD

Patients | Total BMD | L1-L4 | Forearm
--- | --- | --- | ---
Kashman | 30 (CO) | | |
Johnsson | 29 (AO) | | |
Hyer | 60 (CO) | | |
Anido | 7 (CO) | | |
O’Halloran | 12 (CO) | | |
Thoren | 33 (CO-AO) | | |
De Boer | 78 (AO) | | |
Holmes | 28 (AO) | | |
Beshyah | 84 (CO-AO) | | |
Rosen | 95 (CO-AO) | | |
Degerblad | 88 (CO-AO) | | |
Cuneo | 101 (AO) | | |
Murray | 123 (CO-AO) | | |

Adult hypopituitarism/6

Effects of rhGH treatment on BMD

Patients | Duration of rhGH therapy | Effect on BMD
--- | --- | ---
O’Halloran 1993 | 12 (AO) | |
Thoren 1993 | 28 (CO-AO) | 6 |
Vendramini 1993 | 18 (CO-AO) | 6 |
Beshyah 1993 | 28 (CO-AO) | 6 |
Degerblad 1994 | 43 (CO-AO) | 6 |
Holmes 1994 | 28 (AO) | 6 |
Beshyah 1995 | 38 (AO) | 24 |
Johnson 1995 | 44 (AO) | 14 |
Bash 1995 | 38 (AO) | 12 |
Hansen 1996 | 28 (AO) | 12 |
Finkenstedt 1997 | 16 (AO) | 12 |
Cuneo 1998 | 166 (T) | |
Getherstrom 2001 | 118 (AO) | 68 |
Bierren 2005 | 38 (AO) | 68 |
Brenner 2005 | 28 (EI) | 68 |
Arwert 2005 | 26 (EI) | |
Eilander 2012 | 128 (EI) | |

GH deficiency/4

GH deficiency/5

GH deficiency/7
Adult hypopituitarism/7
GHD and clinical fractures

Modified from:
Rosen et al., Eur J Endocrinol 1997
Wuster et al., J Bone Mineral Res 2001

The "iceberg paradigm" for vertebral fractures

5-10% In-patient
40-50% Clinical diagnosis
50 % Unknown

Adult hypopituitarism/8
GHD and prevalent radiological vertebral fractures/1

• 107 adults pts (67 M, 40 F; mean age 47 yrs, range: 16-81) with severe GHD.
  – 65 pts in rhGH treatment
  – 42 pts without rhGH treatment

• 130 control subjects (39 M, 91 F, mean age 58.9 anni, range: 26-82) attending the out-patient clinic of Bone Center of University of Brescia

Modified from: Mazziotti et al., J Bone Mineral Res 2006
The importance of early rhGH treatment

Modified from: Mazziotti et al., J Bone Miner Res 2006.

GHD and prevalent radiological vertebral fractures/2

Prevalence of fractures (%)

Untreated GHD Treated GHD Controls Early treated GHD Late treated GHD Untreated GHD

Prevalence of fractures (%)

Modified from: Mazziotti et al., J Bone Miner Res 2006.

GHD and incident vertebral fractures

Mazziotti et al., Endocrine 2016.

The influence of corticosteroid replacement treatment

rhGH treatment seems to protect the skeleton from the negative effects of glucocorticoid overtreatment.

Mazziotti et al., Eur J Endocrinol 2010.

Glucocorticoid replacement, GHD and fractures

GC replacement/3
Subclinical thyrotoxicosis increases fracture risk in untreated GHD

**Neuroendocrine diseases and bone**

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**Hyperpituitarism/1**

*Acromegaly: Bone turnover*

<table>
<thead>
<tr>
<th>Formation</th>
<th>Resorption</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osteocalcin</td>
<td>U-NTX – CTX-1</td>
</tr>
<tr>
<td>↑ Kaji et al, Clin Endocrinol 2001</td>
<td></td>
</tr>
<tr>
<td>↑ Ezzat et al, JCEM 1993</td>
<td></td>
</tr>
<tr>
<td>↑ Kotzmann et al, JBMR 1993</td>
<td></td>
</tr>
<tr>
<td>↑ Bolonowski et al, JBMR 2006</td>
<td></td>
</tr>
<tr>
<td>↑ Ueland et al, Eur J Endoio 2006</td>
<td></td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>hydroxyprolin – U-DpD</td>
</tr>
<tr>
<td>↑ Stepni et al, Clin Chim Acta 1979</td>
<td></td>
</tr>
<tr>
<td>↑ Kaji et al, Clin Endocrinol 2001</td>
<td></td>
</tr>
</tbody>
</table>

↓ Trabecular bone biomechanical competence (Ueland et al. EJE 2002)
**Hyperpituitarism/2**

**Acromegaly: BMD**

<table>
<thead>
<tr>
<th>Author(s) (Year)</th>
<th>Lumbar spine</th>
<th>Hip</th>
<th>Femur</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diamond (1989)</td>
<td>↓ ‒ ↑</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ho (1992)</td>
<td>↑ ↔ ↔ ‒</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ezzat (1993)</td>
<td>↓ ‒ ‒</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kotzman (1993)</td>
<td>↓ ‒ ↑ •</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kayath (1997)</td>
<td>↔ ↔ ‒</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scillitani (1997)</td>
<td>↑ ‒ ↔ •</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Longobardi (1998)</td>
<td>↓ ‒ ↔ •</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zuidema (1999)</td>
<td>↓ ‒ ↔ •</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Levene (2000)</td>
<td>↓ ‒ ↔ •</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conversano (2000)</td>
<td>↓ ‒ ↔ •</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Madeira (2010)</td>
<td>↓ ↓ ↔ •</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mazziotti (2008)</td>
<td>↓ ‒ ↓ ↔ •</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sucunza (2009)</td>
<td>↓ ‒ ↔ •</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ueland (2006)</td>
<td>↓ ↔ ↔ ↓ •</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vestergaard (2004)</td>
<td>↑ ‒ ↔ •</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bonadonna (2005)</td>
<td>↓ ↓ ↓ ↔ •</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Osteoporosis (T-score ≤ -2.5 SD) occurs in a minority of patients!

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**Hyperpituitarism/3**

**Acromegaly: prevalent radiological vertebral fractures/1**

**Post-menopausal women**

<table>
<thead>
<tr>
<th>GH excess/5</th>
<th>Hyperpituitarism/3</th>
<th>Acromegaly: prevalent radiological vertebral fractures/1</th>
</tr>
</thead>
<tbody>
<tr>
<td>36 women with acromegaly (15 with active disease and 21 with controlled disease)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Bonadonna et al., J Bone Miner Res 2005

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**Hyperpituitarism/4**

**Acromegaly: prevalent radiological vertebral fractures/2**

**Men**

<table>
<thead>
<tr>
<th>GH excess/6</th>
<th>Hyperpituitarism/4</th>
<th>Acromegaly: prevalent radiological vertebral fractures/2</th>
</tr>
</thead>
<tbody>
<tr>
<td>40 men with acromegaly (15 with active disease and 25 with controlled disease; 13 with untreated hypogonadism)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Mazziotti et al., JCEM 2008
Acromegaly: prevalent radiological vertebral fractures

<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Non vertebral (Clinical)</th>
<th>Vertebral (RX)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vestergaard (2002)</td>
<td>↓</td>
<td>-</td>
</tr>
<tr>
<td>Vestergaard (2004)</td>
<td>↑↓</td>
<td>-</td>
</tr>
<tr>
<td>Bonadonna (2005)</td>
<td>-</td>
<td>↑</td>
</tr>
<tr>
<td>Mazzotti (2008)</td>
<td>-</td>
<td>↑</td>
</tr>
<tr>
<td>Wassenaar (2011)</td>
<td>-</td>
<td>↑</td>
</tr>
<tr>
<td>Padova (2011)</td>
<td>-</td>
<td>↑</td>
</tr>
<tr>
<td>Madeira (2013)</td>
<td>-</td>
<td>↑</td>
</tr>
<tr>
<td>Brzana (2013)</td>
<td>-</td>
<td>↑</td>
</tr>
</tbody>
</table>

All cross-sectional studies

Acromegaly: incident radiological vertebral fractures

* p<0.05 vs. control subjects; † p<0.05 vs. controlled/cured disease; ‡ p<0.05 vs. active disease for 1-12 months

Mazzotti et al., JCE&M 2013

Acromegaly: incident radiological vertebral fractures

* p<0.05, vs. control subjects

Mazzotti et al., JCE&M 2013

Hyperpituitarism/5

Acromegaly: prevalent radiological vertebral fractures

Hyperpituitarism/10

Acromegaly: incident radiological vertebral fractures

Hyperpituitarism/11

Acromegaly: incident radiological vertebral fractures

* p<0.05 vs. control subjects

Mazzotti et al., JCE&M 2013
Hyperpituitarism/8

Acromegaly: effects on trabecular structure/1

**Figure 1**: Differences in trabecular bone structure between a normal acromegalic patient and control group. A, trabecular width; B, trabecular thickness; C, trabecular number. Data are presented as mean ± SD.

Madeira et al., JCE&M 2013

Acromegaly: effects on trabecular structure/2

**CBCT**

Giustina et al., Endocrine 2016 in press

GH as anabolic hormone for bone

**But.....too much is bad**

Fracture Risk | Bone Metabolism
---|---
Low | Normal
Normal | High
High | Low

A new paradigm
PRL-oma and bone/3
Clinical fractures (non-vertebral)

Table 6: Gender and age-adjusted comparison of vertebral and non-vertebral fractures. Numbers are expressed as number/percent. The analysis of fractures was performed using the Student’s t-test for independent samples (i.e., a subject may have fractures even when bone density is normal).

<table>
<thead>
<tr>
<th>Fracture Type</th>
<th>Number/Percent</th>
<th>Number/Percent</th>
<th>Number/Percent</th>
<th>Number/Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vertebral</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-vertebral</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

PRL-oma and bone/4
Radiological vertebral fractures/1

Women/1

PRL-oma and bone/5
PRL excess vs. hypogonadism
PRL excess/7

PRL-oma and bone/5
Radiological vertebral fractures/2

Women/2

<table>
<thead>
<tr>
<th>COVARIATES</th>
<th>ODDS RATIO (C.I. 95%)</th>
<th>p-values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.0 (0.96-1.25)</td>
<td>0.17</td>
</tr>
<tr>
<td>Menopausal status</td>
<td>1.0 (0.99-2.63)</td>
<td>0.20</td>
</tr>
<tr>
<td>Duration of disease</td>
<td>1.16 (2.02-2.03)</td>
<td>0.001</td>
</tr>
<tr>
<td>Treatment with cabergoline</td>
<td>0.69 (0.08-8.86)</td>
<td>0.69</td>
</tr>
<tr>
<td>Serum PRL values</td>
<td>1.01 (0.09-1.02)</td>
<td>0.25</td>
</tr>
<tr>
<td>Serum IGF-I values</td>
<td>0.98 (0.97-0.99)</td>
<td>0.03</td>
</tr>
<tr>
<td>BMD T-score</td>
<td>0.52 (0.22-1.23)</td>
<td>0.24</td>
</tr>
</tbody>
</table>

Mazziotti et al., Endocrine 2011

PRL excess/8

PRL-oma and bone/6
Radiological vertebral fractures/3

Males/1

Prevalence of vertebral fractures (%)

![Graph showing prevalence of vertebral fractures]

PRL excess/9

PRL-oma and bone/7
Radiological vertebral fractures/4

Males/2

<table>
<thead>
<tr>
<th>Patients with PRL-oma or fracture</th>
<th>Recalculated</th>
<th>Not Recalculated</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>12</td>
<td>29</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>49 (22-76)</td>
<td>49 (22-76)</td>
<td>0.695</td>
</tr>
<tr>
<td>Parerental status</td>
<td>15 (7.5)</td>
<td>16 (8.0)</td>
<td>0.67</td>
</tr>
<tr>
<td>Duration of disease</td>
<td>7 (3.5)</td>
<td>7 (3.5)</td>
<td>0.64</td>
</tr>
<tr>
<td>High alcohol consumption</td>
<td>0.76</td>
<td>0.76</td>
<td>0.73</td>
</tr>
<tr>
<td>Serum PRL (ng/ml)</td>
<td>74 (74-85)</td>
<td>74 (74-85)</td>
<td>0.08</td>
</tr>
<tr>
<td>BMI T-score in OS</td>
<td>0.25</td>
<td>0.50</td>
<td>0.09</td>
</tr>
<tr>
<td>Sex of individual (male)</td>
<td>0.6</td>
<td>0.04</td>
<td></td>
</tr>
<tr>
<td>Size of adenoma (mm)</td>
<td>16.3 (12)</td>
<td>15.8 (12)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Size of adenoma (mm)</td>
<td>713 (49-1000)</td>
<td>715 (49-1000)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension/0.7</td>
<td>0.51</td>
<td>0.51</td>
<td>0.03</td>
</tr>
<tr>
<td>Hypothyroidism/0.5</td>
<td>0.005</td>
<td>0.005</td>
<td>0.42</td>
</tr>
<tr>
<td>Diabetes mellitus/0.7</td>
<td>0.79</td>
<td>0.79</td>
<td></td>
</tr>
<tr>
<td>Catecholaminergic activity/0.7</td>
<td>0.01</td>
<td>0.01</td>
<td></td>
</tr>
</tbody>
</table>

Mazziotti et al., Endocrine 2011
Di Somma et al., Clin Endocrinol 2002

**Uncoupled bone remodelling**

Minetto et al., Osteoporos Int 2004

**GC excess/1**

**GCs and bone/1**

*Endogenous Cushing’s syndrome: bone turnover*

**GC excess/2**

**GCs and bone/2**

*Endogenous Cushing’s syndrome: BMD*

Minetto et al., Osteoporos Int 2004

**GC excess/3**

**GCs and bone/3**

*Endogenous Cushing’s syndrome: vertebral fractures/1*

Tauchmanova et al., J Clin Endocrinol Metab 2006

**Table 1:** Comparison of bone turnover, bone density, and fractures in patients and controls

<table>
<thead>
<tr>
<th>Variable</th>
<th>HC (yrs)</th>
<th>Adrenal-dependent Cushing’s Syndrome (yrs)</th>
<th>Cushing’s Disease (yrs)</th>
<th>Healthy Control Subjects (yrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T Score</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vertebral fractures</td>
<td>40.2 ± 13</td>
<td>48.0 ± 12</td>
<td>38.5 ± 13</td>
<td>44.5 ± 13</td>
</tr>
<tr>
<td>Lumbar spine</td>
<td>116 ± 55</td>
<td>176 ± 65</td>
<td>156 ± 55</td>
<td>187 ± 65</td>
</tr>
<tr>
<td>Femoral neck</td>
<td>76.5 ± 21</td>
<td>117 ± 41</td>
<td>78.5 ± 21</td>
<td>107 ± 41</td>
</tr>
<tr>
<td>Total T score</td>
<td>1.07 ± 0.57</td>
<td>1.46 ± 0.57</td>
<td>1.68 ± 0.57</td>
<td>2.51 ± 0.57</td>
</tr>
<tr>
<td>Femoral neck T score</td>
<td>0.80 ± 0.57</td>
<td>1.20 ± 0.57</td>
<td>1.02 ± 0.57</td>
<td>1.95 ± 0.57</td>
</tr>
</tbody>
</table>

**Note:** All values are means ± standard deviation.
**GCs and bone/4**

*Subclinical endogenous Cushing’s syndrome: vertebral fractures*

**Table 1:** Odds Ratios for New Vertebral Fractures for Potential Risk Factors Using Logistic Regression Analysis

<table>
<thead>
<tr>
<th>Factor</th>
<th>OR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (1 year increase)</td>
<td>1.23</td>
<td>0.95–1.57</td>
<td>0.111</td>
</tr>
<tr>
<td>BMI (1 kg/m² increase)</td>
<td>1.23</td>
<td>1.00–1.50</td>
<td>0.036</td>
</tr>
<tr>
<td>T-score BMD (1 unit decrease)</td>
<td>2.9</td>
<td>0.89–14.49</td>
<td>0.191</td>
</tr>
<tr>
<td>TBS (1 unit decrease)</td>
<td>1.12</td>
<td>1.01–1.24</td>
<td>0.012</td>
</tr>
</tbody>
</table>

Chiodini et al., J Clin Endocrinol Metab 2009

Morrell et al., J Bone Miner Res 2011

**GCs and bone/5**

*Subclinical endogenous Cushing’s syndrome: Prediction of vertebral fractures*

<table>
<thead>
<tr>
<th>Factor</th>
<th>OR</th>
<th>95% CI</th>
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Vainicher et al., J Bone Miner Res 2012

**GCs and bone/6**

*Endogenous Cushing’s syndrome: Outcome of BMD after cure of disease*

Leong et al., J Bone Miner Res 2007
Endogenous Cushing’s syndrome: vertebral fractures in cured disease

**Neuroendocrine diseases and bone**

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  - PRL excess (prolactinoma)
  - ACTH excess (Cushing’s disease)
- Exogenous Cushing’s syndrome

**GC use in Italy**
**GC use and bone/1**

bone turnover

![Graph showing bone turnover](image)

Dovio et al., J Clin Endocrinol Metab 2004

**GC use and bone/2**

vertebral fractures/1

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Hip</th>
<th>Vertebral</th>
<th>Wrist</th>
<th>Nonvertebral</th>
<th>Any fracture</th>
</tr>
</thead>
<tbody>
<tr>
<td>GC use</td>
<td>65</td>
<td>119</td>
<td>125</td>
<td>119</td>
<td>119</td>
</tr>
<tr>
<td>GC excess</td>
<td>77.0</td>
<td>81.6</td>
<td>80.2</td>
<td>79.9</td>
<td>78.4</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Steinbuch et al., Osteoporos Int 2004

**GC use and bone/3**

vertebral fractures/2

![Graph showing vertebral fractures](image)

Giove-Fedro Study: Angeli et al., Bone 2005
Van Staa, Q. J. Med 2005

GC use and bone/4
vertebral fractures/3

<table>
<thead>
<tr>
<th>GC dose</th>
<th>N</th>
<th>GC use and bone</th>
<th>Veretbral fractures</th>
<th>GC excess</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;2.5 g</td>
<td>5</td>
<td>1.03 (0.58-2.64)</td>
<td>0.67 (0.40-1.20)</td>
<td>2.13 (0.40-11.50)</td>
</tr>
<tr>
<td>2.5-4.9 g</td>
<td>7</td>
<td>1.07 (0.34-3.38)</td>
<td>1.47 (0.57-3.73)</td>
<td>2.32 (0.40-14.00)</td>
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<tr>
<td>5-7.4 g</td>
<td>6</td>
<td>1.07 (0.31-3.48)</td>
<td>1.40 (0.50-3.98)</td>
<td>2.29 (0.40-14.00)</td>
</tr>
<tr>
<td>&gt;7.5 g</td>
<td>4</td>
<td>1.06 (0.31-3.48)</td>
<td>1.31 (0.52-3.38)</td>
<td>2.08 (0.39-11.09)</td>
</tr>
</tbody>
</table>

Van Staa, Q. J. Med 2005

GC use and bone/5
vertebral fractures/4

Table 1: Prevalence and RR of fracture for age, sex, risk factors and indicators for glucocorticoid GC use.

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Prevalence</th>
<th>Clinical osteoporosis fracture RR (95%CI)</th>
<th>Clinical vertebral fracture RR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (for each 10 years of age)</td>
<td>1.67 (1.01-2.77)</td>
<td>2.07 (0.50-9.75)</td>
<td>1.84 (1.12-3.00)</td>
</tr>
<tr>
<td>Sex, male</td>
<td>1.64 (0.90-2.97)</td>
<td>1.90 (0.50-7.52)</td>
<td>1.80 (1.10-2.90)</td>
</tr>
<tr>
<td>smoking history*</td>
<td>1.80 (1.01-3.19)</td>
<td>2.07 (0.50-9.75)</td>
<td>1.84 (1.12-3.00)</td>
</tr>
<tr>
<td>BMI</td>
<td>0.79 (0.53-1.19)</td>
<td>0.90 (0.59-1.38)</td>
<td>0.90 (0.60-1.38)</td>
</tr>
<tr>
<td>Waist*</td>
<td>1.10 (0.59-2.09)</td>
<td>1.05 (0.50-2.20)</td>
<td>1.20 (0.50-3.00)</td>
</tr>
<tr>
<td>Family history of osteoporosis</td>
<td>1.64 (1.01-2.68)</td>
<td>1.90 (0.50-7.52)</td>
<td>1.80 (1.10-2.90)</td>
</tr>
<tr>
<td>Other indicators</td>
<td>1.64 (1.01-2.68)</td>
<td>1.90 (0.50-7.52)</td>
<td>1.80 (1.10-2.90)</td>
</tr>
</tbody>
</table>

Van Staa, Q. J. Med 2005

GC use and bone/6
vertebral fractures/5

Van Staa et al., Arthritis Rheum 2003

Gluocorticoid Therapy • No Glucocorticoid Therapy

<table>
<thead>
<tr>
<th>Lumbar Spine T-score</th>
<th>Femoral Neck T-score</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>15</td>
<td>15</td>
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<tr>
<td>10</td>
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<tr>
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</tbody>
</table>

Van Staa et al., Arthritis Rheum 2003
GC use and bone/7  
vertebral fractures/6

<table>
<thead>
<tr>
<th></th>
<th>BMD &gt; 1 SD</th>
<th>BMD 1-1.9 SD</th>
<th>BMD &lt; 1 SD</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.9</td>
<td>0.94</td>
<td>1.2</td>
<td>1.36 (1.03-1.80)</td>
<td>0.03</td>
</tr>
<tr>
<td>Gender</td>
<td>0.94</td>
<td>0.99</td>
<td>1.1</td>
<td>1.00 (0.71-1.41)</td>
<td>0.99</td>
</tr>
<tr>
<td>BMI</td>
<td>0.94</td>
<td>0.99</td>
<td>1.1</td>
<td>1.00 (0.71-1.41)</td>
<td>0.99</td>
</tr>
<tr>
<td>History of osteoporosis</td>
<td>0.94</td>
<td>0.99</td>
<td>1.1</td>
<td>1.00 (0.71-1.41)</td>
<td>0.99</td>
</tr>
</tbody>
</table>

Vestergaard et al, Calcif Tissue Int 2008

GC use and bone/8  
vertebral fractures after GC withdrawn

![Graph showing OR (95% CI) vs. days from GC withdrawal](image)

Vestergaard et al, Calcif Tissue Int 2008

GC use and bone/9  
Management of GIO: guidelines ACR 2001

- Pts starting therapy with GC > 5 mg/day
  - More than 3 months
  - Change of lifestyle
  - Supplementation with calcium+vit.D
  - BPs
  - T-score < -1.0 SD
  - T-score > -1.0 SD
  - DEXA
  - After 1-2 years
  - BPs+
  - Calcium+Vit. D

- Pts in therapy GC > 5 mg/day
  - Change of lifestyle
  - Supplementation with calcium+vit.D
  - Gonadal hormones (hypogonadism)

ACR, Arthritis Rheum 2001
GC use and bone/10
Management of GIO: ACR guidelines 2010

Counsel and assess risk factors of those starting or on prevalent GC Therapy

Determine patient risk category

Low Risk
- If GCs <7.5 mg/day: no pharmacologic treatment recommended
- If GCs >7.5 mg/day: Alendronate°, risedronate° or zoledronic acid°°

Medium Risk
- If GCs <7.5 mg/day: Alendronate° or risedronate°
- If GCs >7.5 mg/day: Alendronate°, risedronate° or zoledronic acid°°

High Risk
- If GCs <5 mg/day for ≤1 month: Alendronate°, risedronate° or zoledronic acid°°
- If GCs <5 mg/day for >1 month: Alendronate°, risedronate° or zoledronic acid°°
- For ≥1 month: Alendronate°, risedronate°, ral-act°° or tetrabone°°

*Anticipated or prevalent duration of ≥3 months of GCs
°Level of evidence A; °°Level of evidence B

Grossman et al, Arthritis Care Res 2010

GC use and bone/11
Management of GIO: IOF guidelines 2012/1

Low Menopause Status and men ≥50 years of age with T-score <3.5 standard deviation

Counseling and guidance (see text below)

- Complete fracture or T-score ≤3.5 or prevalent GC therapy ≤3 months

- Bone mineral density, age ≥70 yrs, prevalent GC therapy ≥3 months

- Bone density >70% at age expected

- BMD T-score ≤−1.5

- Drug treatment as indicated (see Table 1)

°° treatment are appropriate according to country

Lekamwasan et al, Osteoporos Int 2012

GC use and bone/12
Management of GIO: IOF guidelines 2012/2

Indications for bone-protective therapy in postmenopausal women and men ≥50 years on glucocorticoid therapy

- Aged ≥70 years
- Previous fragility fracture or incident fragility fracture during glucocorticoid therapy
- High doses of glucocorticoids, depending on daily dose and presence or absence of other clinical risk factors
- BMD T-score ≤−1.5

Lekamwasan et al, Osteoporos Int 2012
**Management of GIO: uncertainties**

- Treatment of pre-menopausal women
- Treatment of patients undergoing low-GC therapy
- Predictive factor of lumbar BMD (hip BMD in FRAX)
- Use of teriparatide
- Use of combination therapies
- Duration of treatment with bone-active drugs

Hansen et al., J Bone Miner Res. 2011

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**Neuroendocrine diseases and bone**

**Conclusions**

- Pituitary hormones are important for skeletal health and pituitary diseases are associated with an increased fracture risk.
- BMD is poorly predictive for fracture risk in osteoporosis induced by pituitary diseases.
- The control of pituitary disease is critical for the skeletal health.
- The potential effectiveness of anti-osteoporotic drugs needs to be clarified.