Bisphosphonates in Dentistry

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International Association of Disability in Oral Health
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Antiresorptive Agent-Induced Osteonecrosis of the Jaw (ARONJ)

- Area of exposed bone in maxillofacial region that has been present for more than 8 weeks \(^1\) Khosla et al (2007); JBMR
- Associated with bisphosphonates and denosumab
- Incidence
  - IV bisphosphonates and malignancy (0.8 – 12%)
  - Oral bisphosphonates and osteoporosis (1/1,000-1/10,000)
- Impaired QOL\(^2\) and chronic sequelae
- Often does not resolve in oncology cases

\(^1\)Miksad et al (2011); Oncologist
Nomenclature - ARONJ

• Originally called bisphosphonate-associated osteonecrosis of the jaw (2008 ADA Council advisory statement)

• Since then a few cases of ONJ have been described in patients treated with denosumab for osteoporosis and more in patients treated with denosumab for metastatic breast and prostate cancer

• Antiresportive agent-induced ONJ (2011 statement)

Hellstein JW et al, JADA 2011
Potential Mechanisms of Anti-Resorptive Drugs

A Normal

- Osteoblasts

B Classic antiresorptives

- Osteoblasts

C Uncoupling antiresorptives

- Osteoblasts

Therapeutic Targets in Osteoclast Physiology

Novel Anti-Resorptive Drugs

- **Denosumab**
  - SC human antibody against RANK ligand (stem-cell factor for osteoclasts)
  - Phase 3 study (completed)

- **Odanacatib and ONO-5334**
  - Oral Cathepsin K (osteoclastic enzyme that degrades collagens) inhibitors
  - Phase 3 studies underway

- **Saracatinib**
  - Oral c-src kinase (enzyme involved in osteoclast activation) inhibitor
  - Phase 2 study underway
Denosumab
Denosumab Binds RANK Ligand and Inhibits Osteoclast Formation, Function, and Survival

- **Bone Formation**
- **Bone Resorption Inhibited**

**Osteoclast Formation, Function, and Survival Inhibited**

- CFU-GM → Prefusion Osteoclast
- Osteoclasts
- Osteoblasts

**Pathways**
- RANKL
- RANK
- OPG
- Denosumab

**Factors**
- Hormones
- Growth Factors
- Cytokines
Denosumab Re-treatment and Changes in Serum CTx and BSAP Levels

*Phase 2 Study in Women With Low BMD*


**Serum CTx – Bone Resorption**

**BSAP – Bone Formation**
Frequency of ONJ – Benign Indications

- **Retrospective assessment**
  - ASBMR consensus rep. 1/10,000-1/100,000
  - German study 1/13,500
  - ADA < 1/100,000
  - Canadian study < 1/100,000
  - Kaiser-Permanente 1/952-1/1,537

- **Prospective assessment**
  - HORIZON (>10,000 pts) 2 BP/1 placebo (incl follow up study)
  - 2,000,000 pts used zoledronic acid so far
    - Not a single ONJ case reported

- Risk in oncology trials is much higher 1-2%

- In oncology trials Denosumab has the same risk of ONJ as zoledronic acid – also 4 pts in osteoporosis trial extension
Risk Factors for ARONJ

- Age > 65 yrs
- Periodontitis
- Use of bisphosphonates > 2 yrs
- Smoking
- Denture wearing
- Diabetes mellitus
- Invasive bone procedures such as tooth extractions
Special Considerations Using Intravenous Bisphosphonates in Cancer - ONJ

- ONJ is uncommon, but serious and is also seen rarely with oral amino-bisphosphonates (alendronate, risedronate, ibandronate), and etidronate and clodronate.

- Numbness may also be a feature, but is not mandatory.

- Prevention: Avoid dental procedures, particularly extractions on bisphosphonates, and encourage good dental hygiene.

- Local and systemic antibiotic prophylaxis before extractions.

- Surgical treatment not recommended.
ASBMR and Australian Recommendations on ONJ

- Before prescribing, discuss benefits and risks of bisphosphonates and other treatment options
- Consider dental referral if poor dental hygiene or need for extraction are concerns
- Dentist should minimise need for future dental extractions
- If ONJ is suspected on bisphosphonates, prompt dental referral is required
- If on bisphosphonates and dental extraction required consider stopping for 3 mths before and after extraction
- Low serum CTX is not predictive of ONJ

Antiresorptive Drug Holidays

- “Insufficient evidence to recommend a holiday from Antiresorptive drug therapy or waiting periods before performing dental treatment for prevention of ARONJ”

- “Significant therapeutic benefits of AR agents in patients with osteoporosis far outweigh the small risk of developing ARONJ”

Hellstein JW et al, JADA 2011
Prevention Strategies for Patients Receiving Antiresorptive Therapy

| Prior to therapy | • Optimal time to establish a lifetime oral health awareness as the long-term nature of antiresorptive therapy is associated with ever increasing ARONJ risk  
|                 | • Optimal period to remove unsalvageable teeth and perform invasive dentoalveolar procedures, although a less stringent requirement than with patients using these drugs as part of cancer therapy  
|                 | • With assessment of overall caries risk, periodontal disease risk and “dental IQ” of the patient, the dentist is best qualified to establish an appropriate treatment plan in coordination with the patient and the patient’s physician |
# Prevention Strategies for Patients Receiving Antiresorptive Therapy

## Therapy < 2 years

- The discussions and assessments mentioned above are often NOT performed or even possible prior to the start of antiresorptive therapy, but all remain applicable after treatment has begun.

- Risk in this time period is very low, however, a few such cases of ARONJ have been reported.

- With the possible exception of orthognathic surgery, even dento-alveolar procedures involving periosteal penetration or intramedullary bone exposure (e.g. extractions, apicoectomies, periodontal surgeries, implants or biopsies) seem to carry a minimal risk for ARONJ.

- Chlorhexidine rinses are advised whenever periosteal or medullary bone exposure is anticipated or observed.

- In patients with multiple surgical needs, a trial segmental approach may be helpful in assessing individual patient risk for osteonecrosis and reducing the likelihood of multifocal ARONJ.

## Therapy > 2 years

Continue as above while advising patient and prescribing physician that risk for ARONJ continues to increase with extended drug use.
Prevention Strategies for Patients Receiving Antiresorptive Therapy

<table>
<thead>
<tr>
<th>Any length of therapy</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• It is appropriate for the dentist to discuss antiresorptive therapy as related to the patient's oral health with the patient's physician</td>
<td></td>
</tr>
<tr>
<td>• Discontinuation of antiresorptive therapy should be a medical decision based primarily upon the risk for skeletally related events (e.g. fractures) secondary to low bone density, NOT the potential risk of ARONJ</td>
<td></td>
</tr>
<tr>
<td>• As above, no oral and maxillofacial surgical procedures are strictly contraindicated although treatment plans that minimize periosteal and/or intrabony exposure or disruption are preferred</td>
<td></td>
</tr>
</tbody>
</table>
## Prevention Strategies for Patients Receiving Antiresorptive Therapy

| Risk assessment | Serum CTx levels have not shown reliability or accuracy in predicting risk for ARONJ. Therefore, serum testing is not recommended to predict risk.  
|                 | Though the trial segmental or sextant approach to surgical procedures described above has not been studied in a prospective fashion, it should help limit the extent of ARONJ in a given patient. |
| Emergency dental therapy | All extractions or dento-alveolar surgeries required on the basis of dental or medical emergency are appropriate, regardless of number and multifocality |
| Routine dental care | Good oral health and routine dental care are always recommended |
Bone Turnover Markers Reflect Integrated Skeletal Bone Resorption and Formation

- **Matrix proteins**
  - Osteocalcin (OC)
  - Procollagen type 1 propeptides
    - C-terminal (PICP)
    - N-terminal (PINP)

- **Enzyme**
  - Bone isoform of alkaline phosphatase (bone ALP)

- **Collagen degradation products**
  - Pyridinium crosslinks of collagen
    - C-and N-telopeptides (CTX, NTX)
    - Deoxypyridinoline (DPD)

- **Enzyme**
  - Tartrate-resistant acid phosphatase (TRAP), type Vb

*Delmas PD. J Bone Miner Res 2001; 16: 2370*
Reference Ranges for P1NP in Premenopausal Women

Adapted from slide provided by Eastell R
Sources of Total Variability ($CV_T^2$)

Pre-Analytical Variability ($CV_{PA}^2$)

Diurnal Variability
Intra-Individual Variability

Effects of UV light, temperature
Effects of Food, menstrual cycle

Analytical Variability ($CV_A^2$) - assay precision and accuracy

Between Laboratory Variation

Clowes JA et al, Bone 2002
Specific Conditions
Implant Placement

• Success rates of implants in patients receiving bisphosphonates is no different from those in patients not on bisphosphonates for up to 10 yrs

• AR therapy is not a contraindication to dental implant placement

• Larger, longer-term studies are required
Specific Conditions
Oral and Maxillofacial Surgery

- Conservative surgical technique with primary tissue closure or placement of semipermeable membranes over extraction sites if primary closure not possible
- Chlorhexidine mouth wash twice daily for 4-8 wks
- Antibiotic prophylaxis for one day before and 3-7 days after procedure
- Endodontic treatment is preferred
Specific Conditions
Orthodontics

- Inhibition in tooth movement with AR drugs - case reports
- Orthodontics is not contraindicated
- Longer duration of orthodontic treatment may be required
Background

Background

• Significant burden of disease

• Pathophysiology is poorly understood

• Treatment is often challenging
  – Few validated therapies
Is periodontal disease a risk factor for jaw osteonecrosis in patients taking intravenous bisphosphonates?

Dr Claudine Tsao

Supervisors: A/Prof Darby, Dr G Borromeo, Prof PR Ebeling
NBPs – mechanism of action

• Inhibit farnesyl diphosphate synthase in the HMG-CoAR (or mevalonate) pathway

• Actions on osteoclasts
  ↓ recruitment, differentiation and activity
  ↑ apoptosis

• Actions on osteoblasts, osteocytes

• Inhibit angiogenesis

• Inhibit tumour cells

• Pro-inflammatory
NBPs and inflammation

• Pro-inflammatory

Effects on **IL-1β**, **IL-6** and **TNF-α** investigated in:

• Acute phase response

• **Macrophages**

• Animal models
### NBPs and inflammation – Macrophages

<table>
<thead>
<tr>
<th>Treatment</th>
<th>IL-1β</th>
<th>IL-6</th>
<th>TNF-α</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alendronate</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
<td>Monkkonen 1995</td>
</tr>
<tr>
<td>Alendronate</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
<td>Makkonen 1999</td>
</tr>
<tr>
<td>Alendronate</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
<td>Deng 2008</td>
</tr>
<tr>
<td><strong>BP pre-treatment:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alendronate → LPS</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>Monkkonen 1995</td>
</tr>
<tr>
<td>Alendronate → LPS</td>
<td>↑</td>
<td></td>
<td></td>
<td>Makkonen 1999</td>
</tr>
<tr>
<td>Alendronate → LPS</td>
<td>↑</td>
<td></td>
<td>NE</td>
<td>Monkkonen 1998</td>
</tr>
<tr>
<td>Alendronate →</td>
<td>↑</td>
<td></td>
<td>NE</td>
<td>Deng 1998</td>
</tr>
<tr>
<td><em>P. gingivalis and T. forsythia</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pamidronate → LPS</td>
<td>↑</td>
<td>↑</td>
<td></td>
<td>Pennanen 1995</td>
</tr>
</tbody>
</table>

*NE*: Not evaluated.
ONJ risk factors

- NBP factors
  - zoledronic acid, duration of exposure, no. of infusions
- Precipitants (dental extraction, dentures)
- Age
- Smoking
- Concomitant conditions
  - rheumatoid/osteoarthritis, renal dialysis, low Hb levels
- Concomitant medications
  - chemotherapy, glucocorticoids, anti-angiogenic drugs erythropoetin
- Periodontal disease present in up to 84% of ONJ cases
  (Jadu et al. 2007, Marx 2005, Saussez et al. 2009)
- The association between periodontal disease and ONJ has been disputed
Putative ONJ pathophysiology

- Oversuppression of angiogenesis (Wood 2000, Fournie 2002)
- Altered functioning of oral mucosal cells (Landesberg 2008, Schepper 2009)
- Microbial flora (Hansen 2007)
  - Aggregatibacter actinomycetemcomitans (AA)
- Genetic differences (Sarasquete 2008)
- Pro-inflammatory effect (Santini 2004)
Periodontal disease

Destruction potentiated by cascade of inflammatory mediators:

- IL-1β
- TNF-α
- MMP-8
- IL-6
- TGF-β1
- MMP-9
- IL-8
- PGE$_2$
- MMP-13
AIM

To investigate whether periodontal disease is a risk factor for jaw osteonecrosis in participants with a history of intravenous bisphosphonate exposure for malignancy.
METHODS – Research outline

• Cross-sectional study

• **Exposure**: Periodontal disease

• **Outcome**: ONJ

• **Population**: IV bisphosphonate history for multiple myeloma, or breast and prostate cancer with osseous metastasis

**Recruitment**

**Cases** (ONJ +) from 7 dental specialist departments

**Controls** (ONJ -) from 2 Oncology departments

1 Case : 2 Controls

**Match**: age and gender
Clinical examination

1. Medical history
2. Blood test
3. Oral examination
   - Gingival crevicular fluid sampling
Analysis of GCF

Radioimmunoassay (RIA) for aminoterminal propeptides of Type I collagen (PINP)

Multiplex analysis – 27 Plex
### Multiplex analysis – 27 Plex

<table>
<thead>
<tr>
<th>Category</th>
<th>Cytokines and Growth Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pro-inflammatory</td>
<td>IL-1β, IL-2, IL-6, IL-8, IL-12, IL-15, IL-17&lt;br&gt;TNF-α, IFN-γ, IP-10, MCP-1, MIP-1α, RANTES&lt;br&gt;IL-5, IL-13, Eotaxin, MIP-1β</td>
</tr>
<tr>
<td>Attenuate inflammation</td>
<td>IL-4, IL-10, IL-ra</td>
</tr>
<tr>
<td>Growth factors</td>
<td>VEGF, GM-CSF&lt;br&gt;IL-7, IL-9, bFGF, G-CSF, PDGF-bb</td>
</tr>
</tbody>
</table>
Analysis of serum

Metabolic and hormonal indicators

- Calcium, phosphate, albumin, PTH, Vit D

Bone turnover markers

- P1NP, β-CTX

IgG titres against:

- *Porphyromonas gingivalis, Tannerella forsythia, Treponema denticola, Aggregatibacter actinomycetemcomitans*
RESULTS

Case recruitment
125 records screened
48 potential cases identified
22 cases recruited

Control recruitment
503 records screened
113 potential controls identified
41 controls recruited

n=63

ONJ characteristics
• 32 lesions
• 32% had multiple lesions
• 69% of lesions located in the mandible
• Mean duration 22.7 months (SD 17.4, range 3-67)
• 25% had healed at the time of examination
## Results – Bisphosphonate history

<table>
<thead>
<tr>
<th>Variable</th>
<th>Case</th>
<th>Control</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV NBPs history</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of infusions</td>
<td>Mean 34.2</td>
<td>Mean 35.7</td>
<td>0.525</td>
</tr>
<tr>
<td></td>
<td>(SD 19.0)</td>
<td>(SD 28.1)</td>
<td></td>
</tr>
<tr>
<td>Duration of therapy (months)</td>
<td>Mean 49.3</td>
<td>Mean 53.1</td>
<td>0.696</td>
</tr>
<tr>
<td></td>
<td>(SD 34.8)</td>
<td>(SD 39.6)</td>
<td></td>
</tr>
<tr>
<td>Cumulative ZA dose (mg)</td>
<td>Mean 98.0</td>
<td>Mean 97.7</td>
<td>0.983</td>
</tr>
<tr>
<td></td>
<td>(SD 54.5)</td>
<td>(SD 72.7)</td>
<td></td>
</tr>
<tr>
<td>Cumulative PA dose (mg)</td>
<td>Mean 888</td>
<td>Mean 1,078</td>
<td>0.698</td>
</tr>
<tr>
<td></td>
<td>(SD 1,336)</td>
<td>(SD 2,533)</td>
<td></td>
</tr>
<tr>
<td>Ceased IV NBP at examination</td>
<td>86%</td>
<td>29%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Months since last IV NBP infusion</td>
<td>Mean 23.6</td>
<td>Mean 9.60</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>(SD 19.5)</td>
<td>(SD 19.9)</td>
<td></td>
</tr>
<tr>
<td>Oral BP history</td>
<td>14%</td>
<td>15%</td>
<td>1.00</td>
</tr>
</tbody>
</table>
### Results – Periodontal disease prevalence

<table>
<thead>
<tr>
<th>Variable</th>
<th>Case</th>
<th>Control</th>
<th>Adjusted OR † (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDC-AAP Mod/Severe periodontitis</td>
<td>71%</td>
<td>51%</td>
<td>2.95 (0.70-12.5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>( P=0.140 )</td>
</tr>
<tr>
<td>NCHS periodontitis</td>
<td>71%</td>
<td>26%</td>
<td>13 (2.48-67.8)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>( P=0.002 )</td>
</tr>
</tbody>
</table>

**At least one site with:**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Case</th>
<th>Control</th>
<th>Adjusted OR † (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD ( \geq 4 ) mm</td>
<td>71%</td>
<td>28%</td>
<td>12.3 (2.30-66.1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>( P=0.003 )</td>
</tr>
<tr>
<td>PD ( \geq 6 ) mm</td>
<td>6%</td>
<td>5%</td>
<td>1.91 (0.15-24.7)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>( P=0.619 )</td>
</tr>
<tr>
<td>CAL ( \geq 4 ) mm</td>
<td>94%</td>
<td>85%</td>
<td>2.17 (0.19-25.3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>( P=0.536 )</td>
</tr>
<tr>
<td>PI ( \geq 2 )</td>
<td>53%</td>
<td>59%</td>
<td>0.61 (0.17-2.19)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>( P=0.451 )</td>
</tr>
<tr>
<td>GI ( \geq 2 )</td>
<td>35%</td>
<td>31%</td>
<td>1.33 (0.34-5.24)</td>
</tr>
</tbody>
</table>

† Adjusted for age, gender, diabetes, current smoking and number of sites per participant

**CDC-AAP**: United States Centres for Disease Control and Prevention and the American Academy of Periodontology

**NCHS**: United States National Center for Health Statistics
## Results – Periodontal disease severity

<table>
<thead>
<tr>
<th>Variable</th>
<th>Case Mean (SD)</th>
<th>Control Mean (SD)</th>
<th>Adjusted OR † (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>% of sites per participant:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PD ≥ 4 mm</td>
<td>2.37% (2.22)</td>
<td>1.15% (3.03)</td>
<td>1.20 (0.96-1.50)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>$P=0.101$</td>
</tr>
<tr>
<td>PD 4-5 mm</td>
<td>2.26% (2.14)</td>
<td>1.03% (2.35)</td>
<td>1.32 (1.01-1.73)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>$P=0.044$</td>
</tr>
<tr>
<td>PD ≥ 6 mm</td>
<td>0.04% (0.14)</td>
<td>0.23% (1.34)</td>
<td>0.81 (0.25-2.60)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>$P=0.726$</td>
</tr>
<tr>
<td>CAL ≥ 4 mm</td>
<td>26.6% (25.0)</td>
<td>17.2% (17.6)</td>
<td>1.03 (0.99-1.07)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>$P=0.101$</td>
</tr>
<tr>
<td>Mean PD</td>
<td>1.78 (0.24)</td>
<td>1.73 (0.32)</td>
<td>2.48 (0.31-20)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>$P=0.393$</td>
</tr>
<tr>
<td>Mean CAL</td>
<td>2.75 (1.25)</td>
<td>2.73 (0.63)</td>
<td>0.90 (0.35-2.30)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>$P=0.831$</td>
</tr>
</tbody>
</table>

† Adjusted for age, gender, diabetes and current smoking
Results – Analysis of GCF

n=56 (17 cases:39 controls)

<table>
<thead>
<tr>
<th></th>
<th>Case Mean (SD)</th>
<th>Control Mean (SD)</th>
<th>Adjusted OR † (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-1β</td>
<td>46.0 pg/µL (28.8)</td>
<td>33.8 pg/µL (23.5)</td>
<td>24.7 (1.09-562)</td>
</tr>
</tbody>
</table>

† Adjusted IV NBP infusion in last 3 months, current glucocorticoids, anti-angiogenic drug use and current chemotherapy
## Results – Biochemical parameters and bone turnover markers in serum

<table>
<thead>
<tr>
<th>Variable</th>
<th>Case Mean (SD)</th>
<th>Control Mean (SD)</th>
<th>Adjusted OR † (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium mmol/L</td>
<td>2.38 (0.17)</td>
<td>2.39 (0.12)</td>
<td>0.75 (0.01-59.3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>( P=0.898 )</td>
</tr>
<tr>
<td>Phosphate mmol/L</td>
<td>1.18 (0.22)</td>
<td>1.07 (0.20)</td>
<td>7.18 (0.22-229)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>( P=0.265 )</td>
</tr>
<tr>
<td>25(OH) Vit D ng/mL</td>
<td>65.8 (23.8)</td>
<td>65.7 (26.3)</td>
<td>0.99 (0.96-1.01)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>( P=0.352 )</td>
</tr>
<tr>
<td>PTH pmol/mL</td>
<td>6.05 (3.70)</td>
<td>5.61 (3.86)</td>
<td>1.15 (0.95-1.39)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>( P=0.155 )</td>
</tr>
<tr>
<td>Albumin g/L</td>
<td>35 (5)</td>
<td>37 (4)</td>
<td>0.85 (0.73-0.98)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>( P=0.026 )</td>
</tr>
<tr>
<td>P1NP µg/L</td>
<td>31.8 (22.0)</td>
<td>21.3 (10.8)</td>
<td>71.0 (1.91-2,633)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>( P=0.021 )</td>
</tr>
<tr>
<td>B-CTX-I pg/mL</td>
<td>212 (92)</td>
<td>160 (137)</td>
<td>11.7 (0.89-156)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>( P=0.062 )</td>
</tr>
</tbody>
</table>

† Adjusted for months since last IV NBP infusion, current glucocorticoids and anti-angiogenic drug use
Relationship between gingival crevicular fluid and serum P1NP concentrations

![Graph showing the relationship between GCF and Serum P1NP concentrations](image)

$r=0.63, p=0.002$

Key: GCF: Gingival crevicular fluid; P1NP: Aminoterminal propeptides of Type I collagen.
Bone Turnover Markers in ONJ

- **Gingival crevicular fluid**
  After adjustment of the concentration for elution, mean P1NP levels per participant pooled sample was 675 µg/L (SD 464, range 278–2,375)

- **Serum**
  The mean serum P1NP level was 44.2 µg/L, (range 23.6–109)
  The mean serum β-CTX-I level was 0.39 pg/µL, (range 0.13–1.57)

- **Correlations between bone turnover markers in GCF and serum**
  A significant association was found between GCF and serum P1NP, with r=0.629 (p=0.002)
## Results – Serum IgG titres

<table>
<thead>
<tr>
<th>Bacterial antigen</th>
<th>Case † Mean (SD)</th>
<th>Control † Mean (SD)</th>
<th>Adjusted OR ‡ (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>P. gingivalis</em></td>
<td>0.25 (0.43)</td>
<td>0.09 (0.22)</td>
<td>2.72 (1.19-6.22)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><em>P</em>=0.018</td>
</tr>
<tr>
<td><em>T. denticola</em></td>
<td>0.25 (0.32)</td>
<td>0.20 (0.23)</td>
<td>0.94 (0.52-1.72)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><em>P</em>=0.849</td>
</tr>
<tr>
<td><em>T. forsythia</em></td>
<td>0.41 (0.54)</td>
<td>0.26 (0.32)</td>
<td>1.47 (0.62-3.48)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><em>P</em>=0.376</td>
</tr>
<tr>
<td><em>A. Actinomycetem-comitans</em></td>
<td>0.31 (0.15)</td>
<td>0.28 (0.11)</td>
<td>2.54 (0.07-88.6)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><em>P</em>=0.608</td>
</tr>
</tbody>
</table>

†  Results expressed as ELISA OD$_{405}$ units
‡  Adjusted for age, gender, diabetes, current smoking and edentulism
Results Summary

Periodontal disease was associated with ONJ as measured by:

**Clinical parameters**
- NCHS-defined periodontitis
- At least one site with PD $\geq$ 4 mm
- % of sites per participant with PD 4-5 mm

**Surrogate markers**
- GCF IL-1$\beta$ concentration
- Serum IgG titres against *P. gingivalis*
Discussion – potential underlying mechanisms

• *P. gingivalis* may itself predispose to ONJ via direct effects
• Periodontal disease increases the risk of extraction
• Periodontal disease further increasing remodelling demands on jaw bone and thereby compromising healing
• The pro-inflammatory nature of NBPs
CONCLUSION

• In patients with a history of IV bisphosphonates for malignancy, periodontal disease was associated with bisphosphonate-associated ONJ

• Periodontal disease was measured using clinical parameters, serum Immunoglobulin G titres against Porphyromonas gingivalis and gingival crevicular fluid concentrations of Interleukin-1β.
Teriparatide

- In clinical use for osteoporosis ≈ 10 years
  - Vertebral fracture (RRR 65%)
  - Non-vertebral fracture (RRR 53%)
  - Increased spinal and proximal femur BMD

- Anabolic action: increased osteoblastic activity
  - Increased trabecular bone volume
  - Increased cortical thickness

- May stimulate bone repair
  - Pre-clinical studies: promotes exp-induced fracture healing
  - Benign periodontal disease
Teriparatide

Cheung and Seeman (2010); NEJM
Objectives

• To determine whether 8 weeks of treatment with subcutaneous teriparatide results in ONJ resolution
  – Clinically
  – Radiologically

• Secondary objectives
  – Increases bone formation markers
  – Increases jaw osteoblastic activity
  – Improves QOL
Methodology

- Prospective randomised double-blinded placebo-controlled
- Subcutaneous teriparatide + calcium/vitamin D versus placebo + calcium/vitamin D
- Study size: n = 68
- Inclusion criteria: diagnosis of ONJ
- 12 month follow up
Follow Up Procedures

Wk 0  Wk 4  Wk 8  Wk 12  Wk 24  Wk 36  Wk 52

Intervention  Follow Up

Dental examination
Biochemistry
Bone turnover markers
Cone beam CT
Jaw F-18 fluoride-PET
Bone densitometry
QOL Questionnaire
Cone Beam CT

Jaw F-18 Fluoride-PET

- High spatial resolution
- Reflective of osteoblastic activity
  - Fluoride attaches to hydroxyapatite
- Sensitive for diagnosis of ONJ
- Allows study of differential regional effects of teriparatide

Summary

- ARONJ is a significant health problem in cancer patients but far less common in patients with osteoporosis
  - High burden of disease
  - Lack of validated therapy
- Pathogenesis is *not* fully understood
  - Association of periodontal disease
  - Role of oral microbes?
- Teriparatide holds promise as an effective treatment
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Study participants

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