New therapies in Osteoporosis, Sarcopenia, Frailty and Osteoarthritis

Jonathan D. Adachi MD, FRCPC
Actavis Chair for Better Bone Health in Rheumatology
Professor, Department of Medicine
Michael G. DeGroote School of Medicine
McMaster University
Disclosure of Commercial Support

• Potential for conflict(s) of interest:
  – Jonathan D. Adachi has received payment/funding from Amgen whose product is being discussed in this program.
  – Amgen developed romosozumab a product that will be discussed in this program.
Mitigating Potential Bias

- Potential sources of bias identified in slides 1, have been mitigated by limiting evidence of benefit and side effects to a pivotal RCT
Objectives

• Understand the role of sclerostin in bone metabolism
• Review the results of anti-sclerostin therapy in osteoporosis
• Understand the role of diet and exercise in sarcopenia, frailty and osteoarthritis
What is the role of sclerostin?
Sclerostin, primarily secreted by osteocytes, inhibits bone formation and increases bone resorption

Factors that increase sclerostin include estrogen deficiency, skeletal unloading, and glucocorticoids

Sclerostin inhibits osteoblast differentiation and activity

Sclerostin promotes bone resorption by altering osteoclast-regulating cytokines

Sclerostin decreases bone formation and increases bone resorption by inhibiting Wnt signaling in the osteoblast lineage.

**Effects of Wnt Signaling in Bone (Absence of Sclerostin)**

- Wnts activate the β-catenin pathway to increase bone formation and decrease bone resorption
- Wnts activate TCF-4 and LEF-1 for transcription
- Transcription increases bone formation

**Absence of Wnt Signaling in Bone (Presence of Sclerostin)**

- Sclerostin inhibits activation of the β-catenin pathway to decrease bone formation and promote bone resorption
- Sclerostin inhibits β-catenin degradation
- Decreased bone formation
- Decreased OPG
- Decreased RANKL
- Increased CSF-1

**References**

Humans with genetic sclerostin deficiency have high bone mass

Normal

Sclerosteosis

Sclerosteosis:

- Rare autosomal recessive disease
- Mutations in the SOST gene result in the absence of functional sclerostin
- Results in high bone mass with anecdotal evidence of fracture resistance
- Heterozygous carriers have a milder high bone mass phenotype
- In SOST knockout mice it was confirmed that high bone mass with sclerostin deficiency leads to greater bone strength

Genetically-induced reductions in sclerostin increase bone mass and bone strength, making sclerostin an attractive therapeutic target

Romosozumab is a humanized monoclonal antibody that binds and inhibits sclerostin
Sclerostin inhibition by romosozumab increases bone formation and decreases bone resorption.
Sclerostin antibody increased bone formation

In preclinical studies, sclerostin antibody:

• Increased activity of mature osteoblasts
• Activated modeling-based bone formation by converting bone lining cells to osteoblasts
• Recruited osteoblasts from osteoprogenitors
• Increased bone formation on trabecular and cortical surfaces
• Increased wall thickness in remodeling units
• Rapidly increased bone formation markers

In clinical studies, romosozumab:

• Rapidly increased bone formation markers

Romosozumab Treatment in Postmenopausal Women with Osteoporosis

Romosozumab FRAME Study Design

![Study Design Diagram](image-url)

**Double Blind**
- Romosozumab 210 mg SC QM (N = 3,589)
- Placebo SC QM (N = 3,591)

**Open Label**
- Denosumab 60 mg SC Q6M

**Timeline**
- Month 0 (Loading dose of 50,000–60,000 IU vitamin D)
- Month 6
- Month 12
- Month 18
- Month 24

**Assessments**
- Spine x-rays
- Clinical fracture assessment
### Key Eligibility Criteria and Endpoints

| Inclusion Criteria | • Postmenopausal women age 55–90 years  
|                   | • BMD T-score ≤ −2.5 at the total hip or femoral neck |
| Exclusion Criteria | • BMD T-score ≤ −3.5 at the total hip or femoral neck  
|                   | • History of hip fracture or any severe or more than two moderate vertebral fractures  
|                   | • Recent osteoporosis therapy |
| Co-Primary Endpoints | • Subject incidence of new vertebral fracture through 12 and 24 months |
| Secondary Fracture Endpoints | • Subject incidence of clinical fracture, nonvertebral fracture, and other fracture categories through 12 and 24 months |
Statistical Testing Sequence

New vertebral fracture through Month 12

Clinical fracture through Month 12

Nonvertebral fracture through Month 12

Clinical fracture through Month 24

Nonvertebral fracture through Month 24

Additional endpoints tested in sequence

Co-Primary:
Need statistical significance (≤ 0.05) on both to proceed

Secondary:
Test at $\alpha = 0.05$

Secondary:
Controlled by Hochberg's procedure;
if both $p$-values ≤ 0.05,
claim statistical significance on both;
if larger $p$-value > 0.05,
test smaller one at $\alpha = 0.025$

*Hochberg Y. Biometrika. 1988;75:800-802.*
Study Enrollment Geographic Region (Total N = 7,180)

Central/Latin America 43.0%

Central and Eastern Europe 29.2%

Western Europe, Australia/New Zealand 13.6%

Asia Pacific 11.5%

North America 2.7%
## Baseline Characteristics and Subject Disposition

<table>
<thead>
<tr>
<th></th>
<th>Placebo (N = 3,591)</th>
<th>Romosozumab (N = 3,589)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, mean (SD), years</strong></td>
<td>70.8 (6.9)</td>
<td>70.9 (7.0)</td>
</tr>
<tr>
<td><strong>BMD T-score, mean (SD)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lumbar spine</td>
<td>–2.7 (1.0)</td>
<td>–2.7 (1.0)</td>
</tr>
<tr>
<td>Total hip</td>
<td>–2.5 (0.5)</td>
<td>–2.5 (0.5)</td>
</tr>
<tr>
<td><strong>Prevalent vertebral fracture, %</strong></td>
<td>18.0%</td>
<td>18.7%</td>
</tr>
<tr>
<td>Number of prevalent vertebral fractures, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>13.8%</td>
<td>14.1%</td>
</tr>
<tr>
<td>≥ 2</td>
<td>4.1%</td>
<td>4.6%</td>
</tr>
<tr>
<td><strong>Most severe vertebral fracture grade, %</strong></td>
<td>10.5%</td>
<td>10.5%</td>
</tr>
<tr>
<td>Mild</td>
<td>10.5%</td>
<td>10.5%</td>
</tr>
<tr>
<td>Moderate</td>
<td>7.3%</td>
<td>8.2%</td>
</tr>
<tr>
<td>Prior nonvertebral fracture on or after age 45, %</td>
<td>21.8%</td>
<td>21.7%</td>
</tr>
<tr>
<td><strong>Completed 12-month double-blind period, %</strong></td>
<td>89%</td>
<td>89%</td>
</tr>
<tr>
<td>Completed 24-month study period, %</td>
<td>84%</td>
<td>83%</td>
</tr>
</tbody>
</table>

*N = Number of subjects randomized. Percentages based on number of subjects randomized. Vertebral fracture grade based on Genant semiquantitative scale*
Percent Change in Serum P1NP and CTX with Romosozumab Relative to Placebo Through Month 12

P1NP, romosozumab n = 62, placebo n = 62; CTX, romosozumab n = 61, placebo n = 62. Data presented as bootstrapped median treatment difference and 95% CI.
Lumbar Spine and Total Hip BMD Through Month 12

* $p < 0.001$ compared with placebo. Data are least square means (95% CI) adjusted for relevant baseline covariates.
New Vertebral Fracture Incidence Through Month 12 (Co-Primary Endpoint)

<table>
<thead>
<tr>
<th></th>
<th>Placebo (N = 3,591)</th>
<th>Romosozumab (N = 3,589)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Through Month 6</td>
<td>0.8%</td>
<td>0.4%</td>
</tr>
<tr>
<td>Through Month 12</td>
<td>1.8%</td>
<td>0.5%</td>
</tr>
</tbody>
</table>

RRR = 73%  
*p = < 0.001*

RRR = 46%  
*p = 0.056*

n/N1 = number of subjects with fractures/number of subjects in the primary analysis set for vertebral fractures

*p*-value based on logistic regression model adjusted for age (< 75, ≥ 75) and prevalent vertebral fracture
Time to First Clinical Fracture Through Month 12

Subjects Experiencing Event (%)

Nonvertebral and symptomatic vertebral fracture. Nonvertebral fractures comprised the majority (more than 85%) of clinical fractures.

Kaplan Meier curve based on data through month 24. n = number of subjects at risk for event at time point of interest. P-value based on RRR.

- Placebo (N = 3,591)
- Romosozumab (N = 3,589)

Nonvertebral and symptomatic vertebral fracture. Nonvertebral fractures comprised the majority (more than 85%) of clinical fractures.

Kaplan Meier curve based on data through month 24. n = number of subjects at risk for event at time point of interest. P-value based on RRR.

Nonvertebral and symptomatic vertebral fracture. Nonvertebral fractures comprised the majority (more than 85%) of clinical fractures.

Kaplan Meier curve based on data through month 24. n = number of subjects at risk for event at time point of interest. P-value based on RRR.

Nonvertebral and symptomatic vertebral fracture. Nonvertebral fractures comprised the majority (more than 85%) of clinical fractures.

Kaplan Meier curve based on data through month 24. n = number of subjects at risk for event at time point of interest. P-value based on RRR.

Nonvertebral and symptomatic vertebral fracture. Nonvertebral fractures comprised the majority (more than 85%) of clinical fractures.

Kaplan Meier curve based on data through month 24. n = number of subjects at risk for event at time point of interest. P-value based on RRR.

Nonvertebral and symptomatic vertebral fracture. Nonvertebral fractures comprised the majority (more than 85%) of clinical fractures.

Kaplan Meier curve based on data through month 24. n = number of subjects at risk for event at time point of interest. P-value based on RRR.

Nonvertebral and symptomatic vertebral fracture. Nonvertebral fractures comprised the majority (more than 85%) of clinical fractures.

Kaplan Meier curve based on data through month 24. n = number of subjects at risk for event at time point of interest. P-value based on RRR.

Nonvertebral and symptomatic vertebral fracture. Nonvertebral fractures comprised the majority (more than 85%) of clinical fractures.

Kaplan Meier curve based on data through month 24. n = number of subjects at risk for event at time point of interest. P-value based on RRR.

Nonvertebral and symptomatic vertebral fracture. Nonvertebral fractures comprised the majority (more than 85%) of clinical fractures.

Kaplan Meier curve based on data through month 24. n = number of subjects at risk for event at time point of interest. P-value based on RRR.

Nonvertebral and symptomatic vertebral fracture. Nonvertebral fractures comprised the majority (more than 85%) of clinical fractures.

Kaplan Meier curve based on data through month 24. n = number of subjects at risk for event at time point of interest. P-value based on RRR.

Nonvertebral and symptomatic vertebral fracture. Nonvertebral fractures comprised the majority (more than 85%) of clinical fractures.

Kaplan Meier curve based on data through month 24. n = number of subjects at risk for event at time point of interest. P-value based on RRR.

Nonvertebral and symptomatic vertebral fracture. Nonvertebral fractures comprised the majority (more than 85%) of clinical fractures.

Kaplan Meier curve based on data through month 24. n = number of subjects at risk for event at time point of interest. P-value based on RRR.

Nonvertebral and symptomatic vertebral fracture. Nonvertebral fractures comprised the majority (more than 85%) of clinical fractures.

Kaplan Meier curve based on data through month 24. n = number of subjects at risk for event at time point of interest. P-value based on RRR.
Nonvertebral Fracture Incidence Through Month 12 in Central/Latin America vs Rest-of-World

**Central/Latin America** vs Rest-of-World

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Romosozumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subject Incidence (%)</td>
<td>1.2%</td>
<td>1.5%</td>
</tr>
<tr>
<td>n/N1 =</td>
<td>19/1534</td>
<td>24/1550</td>
</tr>
</tbody>
</table>

**Rest-of-World**

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Romosozumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subject Incidence (%)</td>
<td>2.7%</td>
<td>1.6%</td>
</tr>
<tr>
<td>n/N1 =</td>
<td>56/2057</td>
<td>32/2039</td>
</tr>
</tbody>
</table>

**Latin America**

- Placebo: 1.2% (RR 1.25, 95% CI 0.68-2.27), FRAX 8.7%
- Romosozumab: 1.5%

**Non-Latin America**

- Placebo: 2.7% (RR 0.58, 95% CI 0.37 -0.89, p =0.04), FRAX 17%
- Romosozumab: 1.6%

*Regions excluding Central/Latin America grouped post hoc
n/N1 = number of subjects with fractures/number of subjects in the full analysis set
Other Key Exploratory Fracture Endpoints Through Month 12

- **Nonvertebral**
  - Placebo: 2.1%
  - Romosozumab: 1.6%
  - RRR: 25%

- **Major Osteoporotic**
  - Placebo: 1.8%
  - Romosozumab: 1.1%
  - RRR: 40%

- **Hip**
  - Placebo: 0.4%
  - Romosozumab: 0.2%
  - RRR: 46%

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Romosozumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonvertebral</td>
<td>75</td>
<td>56</td>
</tr>
<tr>
<td>Major Osteoporotic</td>
<td>63</td>
<td>38</td>
</tr>
<tr>
<td>Hip</td>
<td>13</td>
<td>7</td>
</tr>
<tr>
<td>(p) (nominal)</td>
<td>0.096</td>
<td>0.012</td>
</tr>
<tr>
<td>(p) (adjusted)</td>
<td>0.096</td>
<td>NA(^a)</td>
</tr>
</tbody>
</table>

Nonvertebral fractures excludes fractures of the skull, facial bones, metacarpals, fingers, and toes, pathologic fractures and fractures associated with high trauma.

Major osteoporotic fractures: clinical vertebral, hip, forearm, and humerus, excluding pathologic fractures.

\(^a\)Osteoporotic fracture \(p\)-value not adjusted as not part of the testing sequence. \(n\) = number of subjects with fractures.
Key Fracture Endpoints Through Month 12 Excluding Central/Latin America

Placebo (N = 2,057)  Romosozumab (N = 2,039)

**New Vertebral**
- Placebo: 2.3%
- Romosozumab: 0.6%
- RRR = 74%
- p < 0.001

**Clinical**
- Placebo: 3.4%
- Romosozumab: 1.6%
- RRR = 52%
- p < 0.001

**Nonvertebral**
- Placebo: 2.7%
- Romosozumab: 1.6%
- RRR = 42%
- p = 0.012

**Major Osteoporotic**
- Placebo: 2.4%
- Romosozumab: 1.0%
- RRR = 58%
- p < 0.001

**Hip**
- Placebo: 0.5%
- Romosozumab: 0.2%
- RRR = 59%
- p = 0.12

\( n/N1 = \) Number of subjects with fractures/number of subjects in the primary set in Rest-of-World population excluding Central/Latin American region Analyses were post hoc
Serum P1NP and CTX Levels Through Month 24

Data are median and interquartile range. Placebo-to-denosumab n = 62; romosozumab-to-denosumab n = 62 (P1NP), n = 61 (CTX)
Lumbar Spine and Total Hip BMD Through Month 24

Placebo-to-denosumab (N = 61)
Romosozumab-to-denosumab (N = 65)

Lumbar Spine

<table>
<thead>
<tr>
<th>Study Month</th>
<th>Percent Change From Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo vs romosozumab</td>
<td>0.4%</td>
</tr>
<tr>
<td>Open-label denosumab</td>
<td>17.6%*</td>
</tr>
</tbody>
</table>

Total Hip

<table>
<thead>
<tr>
<th>Study Month</th>
<th>Percent Change From Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo vs romosozumab</td>
<td>0.4%</td>
</tr>
<tr>
<td>Open-label denosumab</td>
<td>8.8%*</td>
</tr>
</tbody>
</table>

*p < 0.001 compared with placebo. Data are least square mean (95% CI) adjusted for relevant baseline covariates
Subject Incidence of New Vertebral Fracture Through Month 24 (Co-Primary Endpoint)

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Placebo-to-denosumab</th>
<th>Romosozumab</th>
<th>Romosozumab-to-denosumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Through Year 1</td>
<td>1.8%</td>
<td>0.5%</td>
<td>2.5%</td>
<td>0.6%</td>
</tr>
<tr>
<td>Through Year 2</td>
<td></td>
<td></td>
<td>5%</td>
<td></td>
</tr>
<tr>
<td>Year 2 Alone</td>
<td></td>
<td></td>
<td>0.9%</td>
<td></td>
</tr>
</tbody>
</table>

RRR = 73%  
\( p < 0.001 \)

RRR = 75%  
\( p < 0.001 \)

RRR = 81%  
\( p < 0.001 \)

n/N1 = Number of subjects with fractures/number of subjects in the primary analysis set for vertebral fractures

\( p \)-value based on logistic regression model adjusted for age (< 75, ≥ 75) and prevalent vertebral fracture
Time to First Clinical and Nonvertebral Fracture Through Month 24

Clinical Fractures

Nonvertebral Fractures

RRR = 33%
Adjusted $p = 0.096$
Nominal $p = 0.002$

RRR = 25%
Adjusted $p = 0.057$
Nominal $p = 0.029$

Nonvertebral fractures comprised the majority (more than 85%) of clinical fractures. $n =$ number of subjects at risk for event at time point of interest. $p$-value based on RRR
### Romosozumab Safety Overview

<table>
<thead>
<tr>
<th>Double-Blind Period</th>
<th>Placebo (N = 3,576) n (%)</th>
<th>Romosozumab (N = 3,581) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Subject Incidence of All Adverse Events</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serious Adverse Events</td>
<td>2850 (79.7)</td>
<td>2806 (78.4)</td>
</tr>
<tr>
<td>Adjudicated cardiovascular events</td>
<td>312 (8.7)</td>
<td>344 (9.6)</td>
</tr>
<tr>
<td>Deaths</td>
<td>23 (0.6)</td>
<td>29 (0.8)</td>
</tr>
<tr>
<td>Adjudicated cardiovascular deaths</td>
<td>15 (0.4)</td>
<td>17 (0.5)</td>
</tr>
<tr>
<td>Events Leading to Study Discontinuation</td>
<td>50 (1.4)</td>
<td>44 (1.2)</td>
</tr>
<tr>
<td><strong>Events of Interest</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>0 (0.0)</td>
<td>1 (&lt; 0.1)</td>
</tr>
<tr>
<td>Hypersensitivity</td>
<td>245 (6.9)</td>
<td>242 (6.8)</td>
</tr>
<tr>
<td>Injection-site reactions</td>
<td>104 (2.9)</td>
<td>187 (5.2)</td>
</tr>
<tr>
<td>Atypical femoral fracture</td>
<td>0 (0.0)</td>
<td>1 (&lt; 0.1)</td>
</tr>
<tr>
<td>Osteonecrosis of the jaw</td>
<td>0 (0.0)</td>
<td>1 (&lt; 0.1)</td>
</tr>
<tr>
<td><strong>Subject Incidence of Anti-romosozumab Antibody Formation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Binding antibodies</td>
<td>NA</td>
<td>646 (18.0)</td>
</tr>
<tr>
<td>Neutralizing antibodies</td>
<td>NA</td>
<td>25 (0.7)</td>
</tr>
</tbody>
</table>

N = number of subjects who received ≥ 1 dose of investigational product. **a** Occurring in ≥ 10% of subjects in either group: arthralgia (placebo, 12.0%; romosozumab, 13.0%), nasopharyngitis (placebo, 12.2%; romosozumab, 12.8%), back pain (placebo, 10.6%; romosozumab, 10.5%). **b** Includes adverse events adjudicated positive by an independent adjudication committee. For cardiovascular deaths, includes fatal events adjudicated as cardiovascular-related or undetermined (presumed cardiac-related). **c** Event of interest identified by pre-specified MedDRA search strategy. 7 serious adverse events in romosozumab group vs none in placebo. **e** One event also occurred in the open-label period after receipt of denosumab. **f** Antibody positive postbaseline through month 15 with a negative or no result at baseline. NA = only assessed in romosozumab subjects.
Summary

• Romosozumab for 12 months compared with placebo (RRR):
  – New vertebral fracture: 73% ($p < 0.001$)
  – Clinical fracture: 36% ($p = 0.008$)
  – Nonvertebral fracture: 25% ($p = 0.096$)
    • Among subjects outside of Central/Latin America (post hoc): 42% ($p = 0.012$)

• Over 24 months, romosozumab-to-denosumab compared with placebo-to-denosumab (RRR):
  – New vertebral fracture: 75% ($p < 0.001$)
  – Clinical fracture: 33% (nominal $p = 0.002$; adjusted $p = 0.096$)
  – Nonvertebral fracture: 25% (nominal $p = 0.029$; adjusted $p = 0.057$)
Conclusion

• One year of romosozumab was well-tolerated and reduced vertebral and clinical fracture risk rapidly
• The sequence of romosozumab followed by denosumab appears to be a promising regimen for the treatment of osteoporosis
Healthy Aging
Sarcopenia, Frailty, Osteoarthritis

The effects of diet and exercise
The Microbiome and Musculoskeletal Conditions of Aging: A Review of Evidence for Impact and Potential Therapeutics

Claire J Steves, Sarah Bird, Frances MK Williams, and Tim D Spector

Microbiome

• Gut microbiome describes the genetic material of microorganisms within an animal intestine.

• A wide range of diverse diseases and conditions lying outside the gut have been demonstrated to be associated with an abnormal or dysfunctional microbiome.
Alteration of the Microbiome

• Can be altered by antibiotics
• Energy restriction, high meat/fat diet, and changes in fiber modulate the microbiome
• May be altered by probiotics/prebiotics
Why are they important?

• May cause alterations in the gut flora
  – influencing metabolites produced,
  – releasing short-chain fatty acids,
  – modulating the immune system,
  – increased solubility and absorption of minerals,
  – enhanced barrier function
Frailty and sarcopenia
Effects of the Microbiome

• Frailty has been associated with alterations in the microbiome, in particular core butyrate producing commensals.

• A mouse model of sarcopenia appears to be impacted by specific Lactobacillus strains.
Osteoporosis
Effects of the Microbiome

• Osteoporosis has a substantial inflammatory component that may be affected by changes in the microbiome.

• Probiotics and prebiotics have been linked to improvements in bone density in human and animal studies, indicating that the microbiome may be an important therapeutic target in osteoporosis.

Osteoporosis
Effects of the Microbiome

• Prebiotics increase calcium absorption in adolescents and women, and one demonstrated accompanying increased bone mineralization

• Adolescents given mixed short- and long-chain inulin-type fructans had significantly increased whole body BMC and BMD, compared to placebo

• Most likely because of changes in calcium absorption; however, changes in gut microbiota composition and the immune response may have been responsible

Osteoporosis
Effects of the Microbiome

- Galacto-oligosaccharides (GOS) effect on calcium absorption and fecal microbiota examined.
- Levels of beneficial fecal bifidobacteria were increased in a dose-dependent manner.
- Calcium absorption also increased, but this was independent of dose.
- Microbiota changes accompanied increased calcium absorption in a low calcium diet in adolescent children of both sexes taking a soluble maize fiber compared with control but no changes in markers of bone turnover.
Osteoarthritis
Effects of the Microbiome

• Literature considering the microbiome and the use of pro/prebiotics in OA is sparse
• Lactobacillus casei alone or alongside type II collagen (CII) and glucosamine (GS) was given to arthritic rats
• L. Casei appeared to have synergistic action with CII and GS, effectively reducing pain, cartilage destruction, and lymphocyte infiltration more than the treatment with GS and CII together or separately.
• Co-administration led to reduced expression of numerous pro-inflammatory cytokines and matrix metalloproteinases and upregulation of anti-inflammatory cytokines IL-10 and IL-4.

Conclusion

• The microbiome is a highly plausible target for modulation of diseases of aging owing to its close relationship with the innate and adaptive immune systems.

• It should not be considered in isolation because of the recognized influence of host genetics, geography, diet, and other factors.
Higher Dietary Calcium Intakes Are Associated With Reduced Risks of Fractures, Cardiovascular Events, and Mortality: A Prospective Cohort Study of Older Men and Women

Belal Khan, Caryl A Nowson, Robin M Daly, Dallas R English, Allison M Hodge, Graham G Giles and Peter R Ebeling

Khan et al. JBMR 2015;30:1758–1766
All Cause Mortality

Quartiles of Dietary Calcium Intake

All Cause Mortality
1 – 641 mg/d
2 – 785 mg/d
3 – 899 mg/d
4 – 1,076 mg/d

P for trend = 0.018

Khan et al. JBMR 2015;30:1758–1766
CVD Disease

Quartiles of Dietary Calcium Intake

- Incident CVD
  - 1 – 641 mg/d
  - 2 – 785 mg/d
  - 3 – 899 mg/d
  - 4 – 1,076 mg/d

P for trend = 0.036

Odds Ratio / Hazard Ratio (95% confidence interval)

Khan et al. JBMR 2015;30:1758–1766
Incident Stroke

Quartiles of Dietary Calcium Intake

Incident Stroke
1 – 641 mg/d
2 – 785 mg/d
3 – 899 mg/d
4 – 1,076 mg/d

P for trend = 0.014

Odds Ratio / Hazard Ratio (95% confidence interval)

Khan et al. JBMR 2015;30:1758–1766
Incident Fractures

Quartiles of Dietary Calcium Intake

Incident Fractures
1 – 641 mg/d
2 – 785 mg/d
3 – 899 mg/d
4 – 1,076 mg/d

$P$ for trend $= 0.003$

Khan et al. JBMR 2015;30:1758–1766
Higher dietary calcium intake within the current recommendation is safe and likely to be beneficial to health and to be associated with a decreased risk of all-cause mortality, cardiovascular disease, stroke and fractures
Osteoporosis, Quality of Life and Frailty
The Effect of Fractures on HRQoL from pre-fracture to 36 months post-fracture (Home care and LTC cohorts combined)

Tarride et al BMC Geriatrics 2016
The cumulative effects of serial fractures on HRQoL
Frailty increases after a Major Osteoporotic Fracture

<table>
<thead>
<tr>
<th>Factors</th>
<th>Year 1 post-baseline</th>
<th>Year 2 post-baseline</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>With MOF (n=60)</td>
<td>Without MOF (n=3699)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>P-value</td>
</tr>
<tr>
<td></td>
<td>With MOF (n=48)</td>
<td>Without MOF (n=3457)</td>
<td></td>
</tr>
<tr>
<td>Before MOF¹</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age: mean (SD)</td>
<td>71.9 (9.53)</td>
<td>69.2 (8.74)</td>
<td>0.019</td>
</tr>
<tr>
<td>FI: mean (SD)</td>
<td>0.28 (0.15)</td>
<td>0.24 (0.14)</td>
<td>0.008</td>
</tr>
<tr>
<td>After MOF²</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age: mean (SD)</td>
<td>74.0 (9.50)</td>
<td>70.9 (8.84)</td>
<td>0.017</td>
</tr>
<tr>
<td>FI: mean (SD)</td>
<td>0.37 (0.19)</td>
<td>0.30 (0.17)</td>
<td>0.004</td>
</tr>
<tr>
<td>Change before and after the onset of MOF³</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FI: mean (SD)</td>
<td>0.085 (0.086)</td>
<td>0.067 (0.077)</td>
<td>0.036</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| SD = standard deviation; FI = frailty index; MOF = major osteoporotic fracture.  
¹ For Year 1, information before MOF was collected from baseline; for Year 2, information before MOF was collected from Year 1.  
² For Year 1, information after MOF was collected from Year 2; for Year 2, information after MOF was collected from Year 3.  
³ The change of FI for Year 1 denoted as FI\_{(Year2-baseline)}; the change of FI for Year 2 denoted as FI\_{(Year3-Year1)}.  
Li et al J Bone Miner Res 2016
Frailty Predicts Major Osteoporotic Fracture

<table>
<thead>
<tr>
<th>Factors</th>
<th>Year 2 post-baseline (n=48)</th>
<th>Year 3 post-baseline (n=41)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>p-value</td>
</tr>
<tr>
<td><strong>Changed values</strong>&lt;sup&gt;1&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>1.29 (0.49-3.42)</td>
<td>0.60</td>
</tr>
<tr>
<td>FI</td>
<td>1.38 (0.96-1.94)</td>
<td>0.08</td>
</tr>
<tr>
<td><strong>Absolute measures from previous year</strong>&lt;sup&gt;2&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.99 (0.96-1.03)</td>
<td>0.75</td>
</tr>
<tr>
<td>FI</td>
<td>1.33 (1.12-1.58)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

MOF = major osteoporotic fracture; HR = hazard ratio; CI = confidence interval; FI = frailty index

<sup>1</sup> For Year 2, changed values were from Year 1 minus baseline, denoted as FI<sub>(Year1-baseline)</sub>; for Year 3, changed values were from Year 2 minus Year 1, denoted as FI<sub>(Year2-Year1)</sub>.

<sup>2</sup> For Year 2, information was from Year 1; for Year 3, information was from Year 2.
Frailty Predicts Falls and Mortality

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Year 2 post-baseline</th>
<th>Year 3 post-baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>P-value</td>
</tr>
<tr>
<td><strong>Changed values</strong>&lt;sup&gt;2&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Falls</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>1.05 (0.75-1.46)</td>
<td>0.79</td>
</tr>
<tr>
<td>FI</td>
<td>1.10 (0.97-1.25)</td>
<td>0.15</td>
</tr>
<tr>
<td><strong>Death</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>1.23 (0.98-1.56)</td>
<td>0.081</td>
</tr>
<tr>
<td>FI</td>
<td>1.84 (1.34-2.53)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Absolute measures from previous year</strong>&lt;sup&gt;3&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Falls</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>1.00 (0.99-1.02)</td>
<td>0.85</td>
</tr>
<tr>
<td>FI</td>
<td>1.18 (1.10-1.27)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Death</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>1.06 (1.03-1.10)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FI</td>
<td>1.58 (1.33-1.89)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Summary

• Fractures increase frailty
• Frailty is a predictor of major osteoporotic fractures, falls and mortality
Osteoarthritis
Body Weight!

**Obesity** – caused by unhealthy diets and physical inactivity - is the *strongest preventable risk factor* for the occurrence, progression and effect of large joint OA.
What can be done?

The **OBVIOUS** answer – **LOSE WEIGHT** and **EXERCISE**!
Progress of participants through the Arthritis, Diet, and Activity Promotion Trial (ADAPT).

Mean SEM unadjusted Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) physical function summary scores across the 18-month intervention period. $P \ 0.05$, diet plus exercise group versus healthy lifestyle group.

Six Minute Walk Distance

<table>
<thead>
<tr>
<th>Study group</th>
<th>Baseline</th>
<th>6 months</th>
<th>18 months</th>
<th>Change from baseline at 18 months (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy lifestyle</td>
<td>434.61 ± 10.96</td>
<td>428.56 ± 12.88</td>
<td>429.89 ± 12.77</td>
<td>-4.72 (-29.75, 20.31)</td>
</tr>
<tr>
<td>Diet only</td>
<td>425.98 ± 10.89</td>
<td>433.68 ± 11.94</td>
<td>435.63 ± 12.88</td>
<td>9.65 (-15.79, 35.09)</td>
</tr>
<tr>
<td>Exercise only</td>
<td>424.15 ± 11.42</td>
<td>465.04 ± 12.13</td>
<td>472.73 ± 13.12†</td>
<td>48.58 (22.87, 74.29)</td>
</tr>
<tr>
<td>Diet plus exercise</td>
<td>416.15 ± 11.34</td>
<td>482.37 ± 12.65</td>
<td>477.76 ± 13.12†</td>
<td>61.61 (35.90, 87.32)</td>
</tr>
</tbody>
</table>

* Values are the mean ± SEM.
† P < 0.05 versus healthy lifestyle.

Six-minute walk distance at baseline, 6 months, and 18 months and absolute change from baseline*

# Stair-Climb Time

Stair-climb time at baseline, 6 months, and 18 months and absolute change from baseline*

<table>
<thead>
<tr>
<th>Study group</th>
<th>Baseline</th>
<th>6 months</th>
<th>18 months</th>
<th>Change from baseline at 18 months (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy lifestyle</td>
<td>9.59 ± 0.64</td>
<td>9.97 ± 0.75</td>
<td>9.37 ± 0.76</td>
<td>−0.22 (−1.71, 1.27)</td>
</tr>
<tr>
<td>Diet only</td>
<td>9.74 ± 0.65</td>
<td>9.88 ± 0.70</td>
<td>8.43 ± 0.78</td>
<td>−1.31 (−2.84, 0.22)</td>
</tr>
<tr>
<td>Exercise only</td>
<td>10.52 ± 0.66</td>
<td>8.87 ± 0.73</td>
<td>8.89 ± 0.78</td>
<td>−1.63 (−3.16, −0.10)</td>
</tr>
<tr>
<td>Diet plus exercise</td>
<td>10.99 ± 0.67</td>
<td>8.83 ± 0.78</td>
<td>8.45 ± 0.81†</td>
<td>−2.54 (−4.13, −0.95)</td>
</tr>
</tbody>
</table>

* Values are the mean ± SEM.
† P < 0.05 versus healthy lifestyle.

Self Reported Pain

<table>
<thead>
<tr>
<th>Study group</th>
<th>Baseline</th>
<th>6 months</th>
<th>18 months</th>
<th>Change from baseline at 18 months (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy lifestyle</td>
<td>7.25 ± 0.39</td>
<td>6.19 ± 0.46</td>
<td>6.02 ± 0.45</td>
<td>-1.23 (-2.11, -0.35)</td>
</tr>
<tr>
<td>Diet only</td>
<td>6.58 ± 0.40</td>
<td>5.10 ± 0.43</td>
<td>5.51 ± 0.45</td>
<td>-1.07 (-1.95, -0.19)</td>
</tr>
<tr>
<td>Exercise only</td>
<td>6.64 ± 0.39</td>
<td>6.22 ± 0.45</td>
<td>6.24 ± 0.47</td>
<td>-0.40 (-1.32, 0.52)</td>
</tr>
<tr>
<td>Diet plus exercise</td>
<td>7.27 ± 0.41</td>
<td>5.47 ± 0.47</td>
<td>5.07 ± 0.47†</td>
<td>-2.20 (-3.12, -1.28)</td>
</tr>
</tbody>
</table>

* Values are the mean ± SEM scores (range 0–20, with higher scores indicating greater dysfunction). WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.
† P = 0.05 versus healthy lifestyle.

Self-reported pain at baseline, 6 months, and 18 months and absolute change from baseline*
Key Results of “ADAPT”

- Exercise + diet group had significant improvements in pain, 6-minute walk and stair climb time vs. control.
- Exercise only group had significant improvements in walking distance than healthy lifestyle.
- Exercise + diet group had 24% physical function improvement, 18% improvement in diet group.
- Exercise + diet group had 30.3% pain improvement at 6 months with benefits maintained after 18 months.

Conclusion

Exercise and a healthy diet are the mainstays of healthy aging.