Effects of Exercise & Pharmacological Therapy on Bone Density in Persons Post-Stroke
Outline of Presentation

• Introduction
• Methods
• Results
• Discussion of findings
• Clinical Implications
• Limitations of Included studies
Bone loss post stroke

- BMD is decreased by 20-24%\textsuperscript{1}
- Bone loss is a result of a high turn-over of bone with a disproportionate elevation of bone resorption\textsuperscript{2, 3}
- Minimizing bone loss after stroke is critical in reducing the risk of fractures
Mechanisms of Bone Loss post stroke

- There are 4 main mechanisms that contribute to bone loss post stroke\textsuperscript{2-7}:

1. Disuse due to paralysis
2. Vitamin D deficiency due to malnutrition, lack of sunlight exposure and immobilization induced hypercalcemia
3. Compensatory hyperparathyroidism
4. Vitamin K deficiency also due to malnutrition
Falls and fractures

- Reduced BMD makes stroke patients more susceptible to fracture resulting from falls\(^8\)

- Patients with previous stroke constitute a large subgroup among patients with hip fracture
  - They must be considered to be of special interest in the prevention of falls and osteoporosis
Falls Risk & Fracture Post-Stroke

- More than 1/3 of stroke patients suffer a fall during their rehabilitation stay\(^9\)

- Reasons for Falls\(^9\)
  - Deterioration in fall-protective reactions due to changes in intrinsic mechanisms:
    - Impaired balance
    - Postural instability
    - Impaired mobility
    - Cognitive impairment
Implications of Fractures in the stroke population

- Economic perspective
  - The incidence of hip fractures is 2-4 times higher in stroke patients compared to healthy normals\textsuperscript{9, 10}
  - more than 2/3 of patients experience paresis post-stroke and that fractures mainly occur on the paretic side\textsuperscript{10}
  - The cost of a hip fracture has been estimated as $20,000 in the first year after fracture\textsuperscript{11}

- Patient perspective
  - Quality of Life
Treatment of Low BMD Post-Stroke

• Low BMD can be modified through different treatment options:
  • Pharmacological interventions
    – Bisphosphonates
    – Non-Bisphosphonates
  • Exercise therapy
Pharmacological Intervention – Bisphosphonates

• Bisphosphonates inhibit bone resorption through their effects on osteoclast recruitment, differentiation and action\textsuperscript{12}

  – Bisphosphonates in the included studies:
    • etidronate
    • risedronate
    • zolendronate
Pharmacologic Therapy – Non-Bisphosphonates

• There are numerous types of non-bisphosphonates that have been associated with effects on BMD

  – Non-bisphosphonates in the included studies:
    • Salmon calcitonin
    • Ipriflavone
    • Vitamin D
    • Calcium
    • Menatetrenone (vitamin K)
Exercise Therapy

- It has been shown that regular exercise is beneficial for bone health in the chronic stroke population\textsuperscript{13}
- Exercise involving high impact loads positively influences skeletal bone mineral accrual and/or causes improvements in the structural characteristics of bone\textsuperscript{14,15}
Knowledge Gap

• There was no comprehensive systematic review investigating the effects of pharmacological and exercise interventions on BMD in the stroke population

• There was a need for a systematic review to summarize the literature on the effect of pharmacological and exercise interventions on BMD post-stroke
METHODS
of the Review
Eligibility Criteria

• Pharmacological studies
  – Administration of a medication/supplement expected to improve BMD or to attenuate BMD loss

• Exercise studies
  – Type and dose that could be expected to impact BMD or bone geometry
  – Control intervention had to be either:
    • Nothing, a sham/placebo
    • Therapy that was not expected to impact BMD or bone geometry
Eligibility Criteria

• Participants
  – Human subjects who had experienced a stroke
    • Acute stroke = less than one year
    • Chronic stroke = greater than one year

• Outcome measures
  – Validated, reliable, and standardized measure of BMD and/or bone geometry
    • DXA, CXD or pQCT
A literature search was conducted using multiple electronic databases:

- OVID MEDLINE
- OVID EMBASE
- CINAHL
- PEDro
Study Identification

• A grey literature search was performed with the use of:
  – Google
  – Google Scholar

• Archival searches of all journals from which articles were retrieved by the original search

• Exploring the references from those articles originally retrieved
Qualitative Assessment

• Two methods were used to evaluate each article’s quality and level of evidence:
  – RCTs:
    • PEDro scale
    • Sackett's modified Levels of Evidence
  – Non-RCTs:
    • Ten point scale developed using the evaluation criteria set out by the CDR
    • Sackett's modified Levels of Evidence
Quantitative Assessment

• The SES and a 95% CI were calculated for each study that contained the required information

• The SES were classified as:
  – trivial (<0.2)
  – small (0.2-0.5)
  – medium (0.5-0.8)
  – large (≥0.8)
RESULTS
OVID MEDLINE → Literature search

OVID EMBASE

4049 Titles

33 Abstracts

19 Full text articles

CINAHL

12 Included studies
Bisphosphonate Results

- Poole et al. (2007)$^{16}$
  - Intervention: zoledronate
  - $n = 14$
  - PEDro = 9
  - Results: Intervention group
    - Did not experience the ↓ in BMD on the hemiplegic side
    - Experienced an ↑ in BMD on the non-hemiplegic side
Bisphosphonate Results

- Sato et al. (2005)\textsuperscript{17} females
  - Intervention: risedronate
  - $n = 173$
  - PEDro = 9
  - Results: Intervention group
    - Significant $\uparrow$ in BMD on the hemiplegic side
      ($SES = 2.96$)
    - Significant $\uparrow$ in BMD on the non-hemiplegic side
      ($SES = 0.93$)
Bisphosphonate Results

• Sato et al. (2005)\textsuperscript{18} males
  – Intervention: risedronate
  – n = 134
  – PEDro = 8
  – Results: Intervention group
    • Significant ↑ in BMD on the hemiplegic (SES = 3.2)
    • Significant ↑ in BMD on the non-hemiplegic side (SES = 0.69)
Bisphosphonate Results

• Sato et al. (2000)\textsuperscript{19}
  – Intervention: etidronate
  – \( n = 46 \)
  – PEDro = 7
  – Results:
    • Etidronate attenuated the ↓ in BMD on the hemiplegic side (SES = 0.66)
    • No significant change in BMD on the non-hemiplegic side
Bisphosphonate Results

- Ikai et al. (2007)\textsuperscript{20}
  - Intervention: etidronate
  - $n = 35$
  - PEDro = 3
  - Results: Intervention group
    - Smaller ↓ in BMD in the low ADL group on the hemiplegic side (SES = 0.84)
    - No significant change in BMD in the high ADL group on the hemiplegic side or in the low or high ADL group on the non-hemiplegic side
Non-Bisphosphonate Results

• Sato et al. (1997)\textsuperscript{21}
  – Intervention: 1α(OH)D\textsubscript{3} (vitamin D\textsubscript{3})
  – n = 30
  – PEDro = 9
  – Results:
    • Vitamin D\textsubscript{3} prevented a ↓ in BMD on the hemiplegic side (SES = 0.86)
    • No significant changes on the non-hemiplegic side
Non-Bisphosphonate Results

• Uebelhart et al. (1999)\textsuperscript{22}
  – Intervention: salmon calcitonin
  – \( n = 11 \)
  – PEDro = 6
  – Results: Intervention group
    • No significant difference in biochemical bone markers (BMD not measured)
Non-Bisphosphonate Results

• Sato et al. (1998)\textsuperscript{23}
  – Intervention: menatetrenone (vitamin K)
  – \( n = 51 \)
  – PEDro = 5
  – Results: Intervention group
    • Significant \( \uparrow \) in BMD on the hemiplegic side (SES = 1.01)
    • The intervention attenuated the \( \downarrow \) in BMD on the non-hemiplegic side (SES = 0.55)
• Sato et al. (1999)\textsuperscript{24}
  – Intervention: ipriflavone or vitamin D\textsubscript{3}
  – n = 30 and 32
  – PEDro = 5
  – Results:
    • Ipriflavone attenuated the ↓ in BMD compared to both the vitamin D\textsubscript{3} and control groups on the hemiplegic side (SES = 0.79)
    • No significant difference between all groups on the non-hemiplegic side
Exercise Results

• Pang et al. (2005)$^{25}$
  – Intervention: 19 week exercise program; 3x/week
  – n = 30
  – PEDro = 8
  – Results: Intervention group
    • Did not experience the ↓ in BMD on the hemiplegic side (significant result) (SES = -0.11)
    • No significant difference in BMD on the non-hemiplegic side
Exercise Results

• Pang et al. (2006)\textsuperscript{26}
  – Intervention: 19 week exercise program; 3x/week
  – n = 30
  – PEDro = 6
  – Results: Intervention group
    • Significant ↑ in trabecular BMC (SES = 0.48) and cortical thickness (SES = 0.07) on the hemiplegic side
    • Non-significant ↑ on the non-hemiplegic side
Exercise Results

• Liu et al. (1999)\textsuperscript{27}
  – Intervention: stroke rehab exercise program; 5x/week, median length of 105.5 days
  – $n = 80$
  – Cohort quality score = 9
  – Results:
    • Discharge BMD was significantly lower than the BMD at admission for all sites except the unaffected radius, whole upper limb, and whole lower limb
Ikai et al. (2001)\textsuperscript{20}

- Intervention: stroke rehab exercise program; 5x/week for 3 months
- $n = 37$
- Cohort quality score = 7
- Results:
  - High ADL group experienced a significantly smaller ↓ in BMD compared to the low ADL group on the hemiplegic side (SES = 0.80)
  - No significant difference in BMD between the groups on the non-hemiplegic side
DISCUSSION
Bisphosphonate Studies

• All studies showed that either:
  – Treatment group experienced an increase in BMD on the hemiplegic side compared to the control group\textsuperscript{17, 18}
    • These studies had the largest effect sizes
  – Treatment group experienced a smaller decrease in BMD on the hemiplegic side compared to the control group\textsuperscript{16, 19, 20}
Bisphosphonate studies

- Bisphosphonate administration was also found to have an effect on the non-hemiplegic side
  - Three of the five studies using bisphosphonates showed an increase in BMD in the non-hemiplegic limb\textsuperscript{16-18}
  - Two studies reported no decrease in BMD in the intervention group when compared to controls\textsuperscript{19, 23}
Bisphosphonate Studies

• Implication:
  – bisphosphonate interventions have potential to beneficially affect bone metabolism in both the hemiplegic and non-hemiplegic side
Non-bisphosphonate Studies

- 75% of studies demonstrated beneficial effects of BMD on the hemiplegic side\textsuperscript{21, 23, 24}

- Only 1 study found that the treatment (menatetrenone) attenuated, but did not prevent BMD loss on the non-hemiplegic side\textsuperscript{23}
Non-Bisphosphonate Studies

• Implication:
  – non-bisphosphonates appear to have the potential to maintain BMD on the hemiplegic side
  – non-bisphosphonates appear less able than bisphosphonates to affect BMD on the non-hemiplegic side
Biochemical Markers

• When both BMD & biochemical markers were measured, the markers of bone turnover mirrored the changes in BMD on both the hemiplegic and non-hemiplegic side
  – approached reference values in treatment groups & remained abnormal in control groups

• One study only measured biochemical markers and found no significant difference between treatment & control groups$^{22}$
Challenges of Comparing Pharmacological Studies

- Variety of drugs administered
  - each pharmacological intervention is featured in only two studies at the most, therefore not a large body of evidence to support the use of one drug over another

- Variations in:
  - Dose
  - Administration route
  - Length of intervention
Exercise studies

• Two RCTs showed that BMD and/or BMC in the hemiplegic lower limb was maintained in the intervention group, while it decreased in the control group.\textsuperscript{25, 26}
Exercise Studies

• A similar trend was seen in the cohort study carried out by Ikai et al.
  – participants with higher ADL functioning (and assumed higher levels of physical activity) maintained higher BMD on the hemiplegic side than participants with low ADL functioning\textsuperscript{20}

• The cohort study by Liu et al. did not see a beneficial effect of the intervention on BMD
  – likely because exercise program was not of sufficient intensity to stimulate bone remodeling\textsuperscript{27}
• **Implication**: exercise may be able to prevent BMD loss on the hemiplegic side, but appears less able to affect BMD on the non-hemiplegic side
Comparing Pharmacological & Exercise Studies

- Smaller effect sizes were found for the exercise studies in comparison to the pharmacological studies
  - May be due to:
    - a difference in the effectiveness of the treatment
    - confounding factors such as:
      » lower study quality
      » shorter study duration
      » fewer participants
      » variations in type of exercise
Comparing Pharmacological & Exercise Studies

- Measurement sites varied between studies, making direct comparison difficult
  - Most pharmacological studies measured BMD at the second metacarpal, rather than at the hip
Study Limitations

• Sato et al.\textsuperscript{2-7} have found that BMD in post-stroke patients can be influenced by a number of factors including:
  – disuse due to paralysis
  – deficiencies in both vitamin D and K due to malnutrition
  – lack of sunlight exposure

• None of the studies monitored or controlled all of these extraneous factors
Study Limitations

- Stroke duration: Time since stroke for the included patients varied between the studies
  - Acute vs. chronic vs. strokes of varying duration
    - Mechanisms of bone loss may be different between these sub-populations
    - Response to a given treatment may vary between the groups
Study Limitations

- The most common BMD measurement site in the pharmacological studies was the second metacarpal using CXD
  - Easier and more cost effective, but the use of DXA to evaluate BMD is the current ‘gold standard’
  - Since hip fracture is the outcome of interest, best evidence would be provided by using DXA to measure BMD at the hip
Hip Fracture

- Goal is to reduce number of fractures
- The effectiveness of an intervention can be measured by BMD, but an increase in BMD is irrelevant if a fragility fracture still occurs
Clinical implications

- Only two of the studies in this review\textsuperscript{17, 18} used hip fracture incidence as an outcome measure as opposed to an adverse event.

- These two studies showed:
  - Number of falls was approximately the same in both the intervention group and controls.
  - Number of fractures in the intervention group was significantly less than in the control group.
Hip Fracture

• The remaining studies only reported hip fracture as an **adverse event**, rather than as an outcome measure:
  – In the pharmacological studies a higher incidence of hip fractures was reported in the control groups compared to the intervention groups
  – There were no reported fractures in the exercise studies

• May be due to an improvement in fall-protective reactions and/or shorter study duration
Future Directions

• Need for studies that include:
  – long-term follow-up measurement
  – methodological consistency
  – longer duration RCTs for exercise interventions
  – greater number of subjects for exercise studies
  – clear definitions of exercise interventions
  – the combined effects of pharmacological & exercise interventions
  – hip fracture as an outcome measure
Future Directions

• Future studies will help determine:
  – potential adverse effects of pharmacological therapy
  – the most beneficial pharmacological treatment
  – ideal dosage and treatment schedules
  – ideal exercise parameters
Conclusion

• Both pharmacological and exercise treatment show promise
  – Based on the current literature, pharmacological treatment, especially bisphosphonates, appear to be more effective than exercise therapy in maintaining BMD post-stroke
  – However, exercise has benefits that stretch beyond BMD maintenance and should always be included in stroke rehabilitation
Thank You

• To Janice Eng and Maureen Ashe for their guidance and feedback throughout the course of this project
• Thank you for your attention and don’t forget to drink your milk and weight-bear!
References

<table>
<thead>
<tr>
<th>Reference</th>
<th>Details</th>
</tr>
</thead>
</table>
References


