BISPHOSPHONATE USE AND THE RISK OF SUBTROCHANTERIC OR FEMORAL SHAFT FRACTURES

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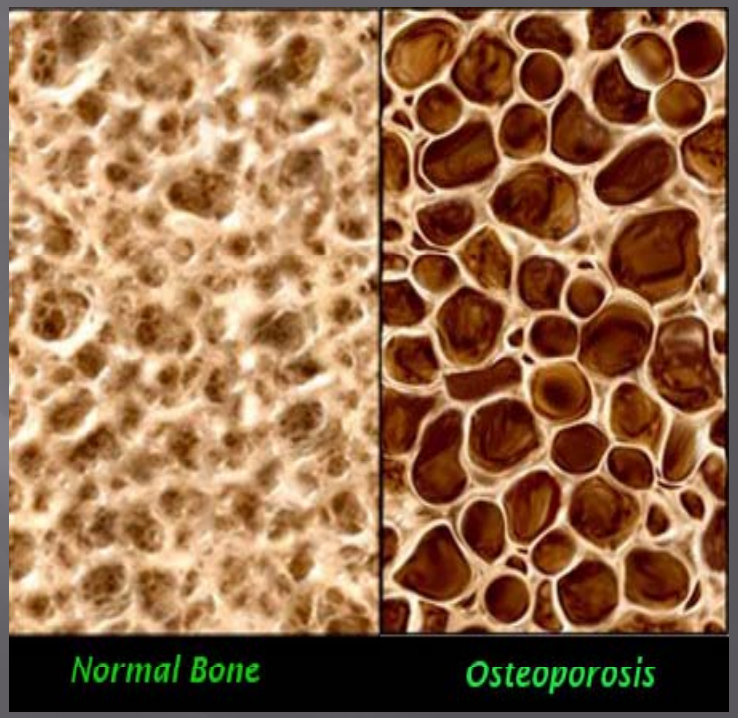
Overview

- Osteoporosis is a disease which has a significant morbidity and mortality.
- 50% of women over 50 years will have an osteoporosis related fracture during their lifetime, and for 1 out of 5 patients with an osteoporosis related fracture, this will result in death within a year.



Treatment of Osteoporosis

- Long term studies have shown that treatment with bisphosphonates reduces the risk of osteoporotic fractures.

- Nonetheless, concerns have arisen that bisphosphonates may play a role in suppressing bone remodeling and causing a decrease in bone strength.

Atypical Vs. Typical Fractures

- Atypical Fractures: fractures involving the subtrochanteric or shaft region of the femur
- These fractures are known as atypical because of their location and radiographic appearance

4 major features of atypia

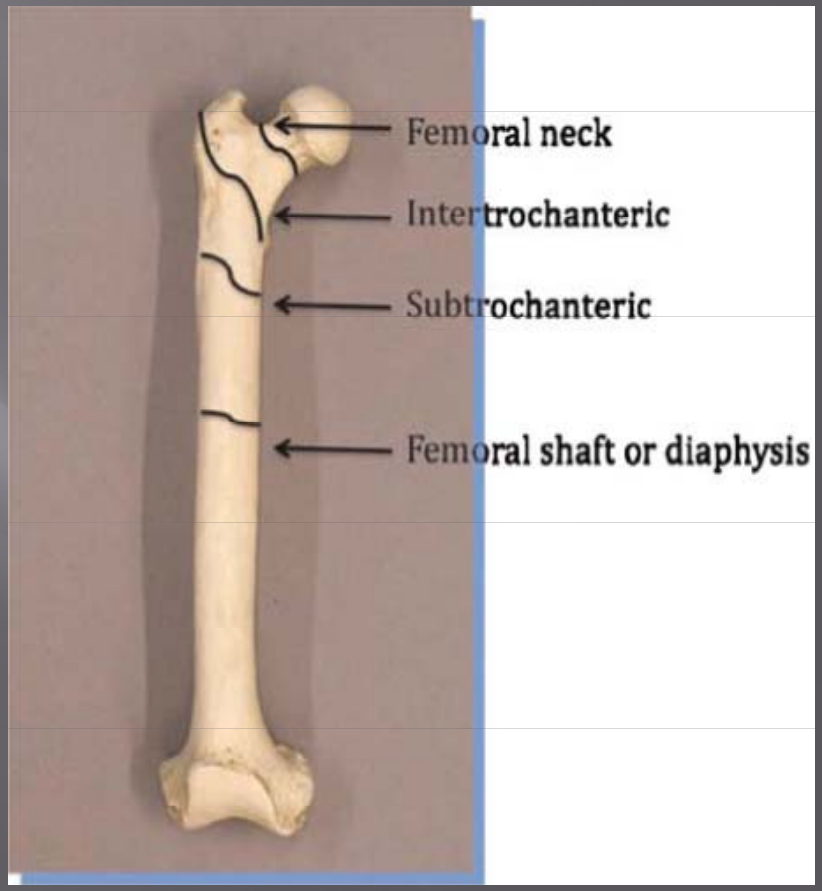
Atypical Femoral Fracture: Major features

Located anywhere along the femur from just distal to the lesser trochanter to just proximal to the supracondylar flare

Associated with no trauma or minimal trauma, as in a fall from a standing height or less

Transverse or short oblique configuration

Complete fractures extend through both cortices and may be associated with a medial spike; incomplete fractures involve only the lateral cortex.



Example of Atypical Fracture

- This is an atypical fracture involving the shaft region of the femur

Study Design

- This study was a population based, nested case-control study
- The population studied association between bisphosphonate use and atypical fractures in a cohort of Ontario women aged 68 years or older.

Study Demographics

- All the women in the study had universal free access to Canadian healthcare services, including hospital care, physician services, and prescription drugs.
- The date of first prescription of bisphosphonate served as the cohort entry date.

Exclusion Criteria

- History of cancer in the past 10 years
- History of diseases affecting bone integrity including osteomalacia, osteopetrosis, hyperparathyroidism, paget's disease, and others.
- History of gastric bypass
- Use of raloxifene, calcitonin, zoledronic acid, or pamidronate in the preceding year

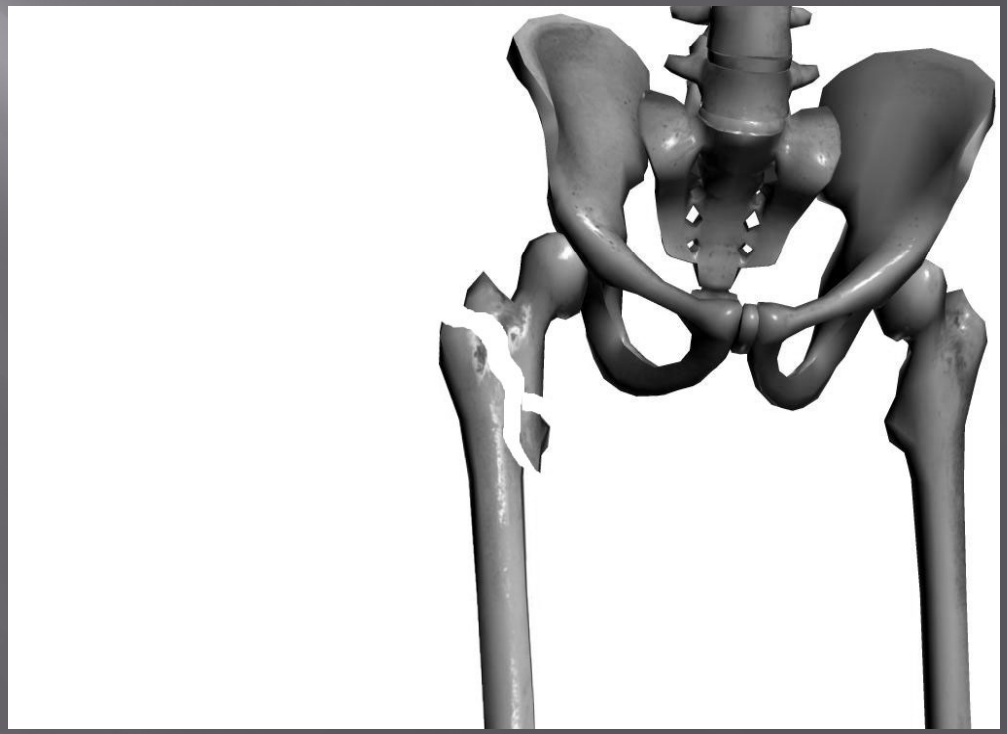
Cases and Controls

- Cases: women who were hospitalized with a subtrochanteric or femoral shaft fracture between April 1 2003 and March 31, 2009
- (women who had fractures due to trauma and MVAs were excluded)

- Controls: For each case, 5 controls were selected from the cohort who was not hospitalized with a subtrochanteric or femoral shaft fracture

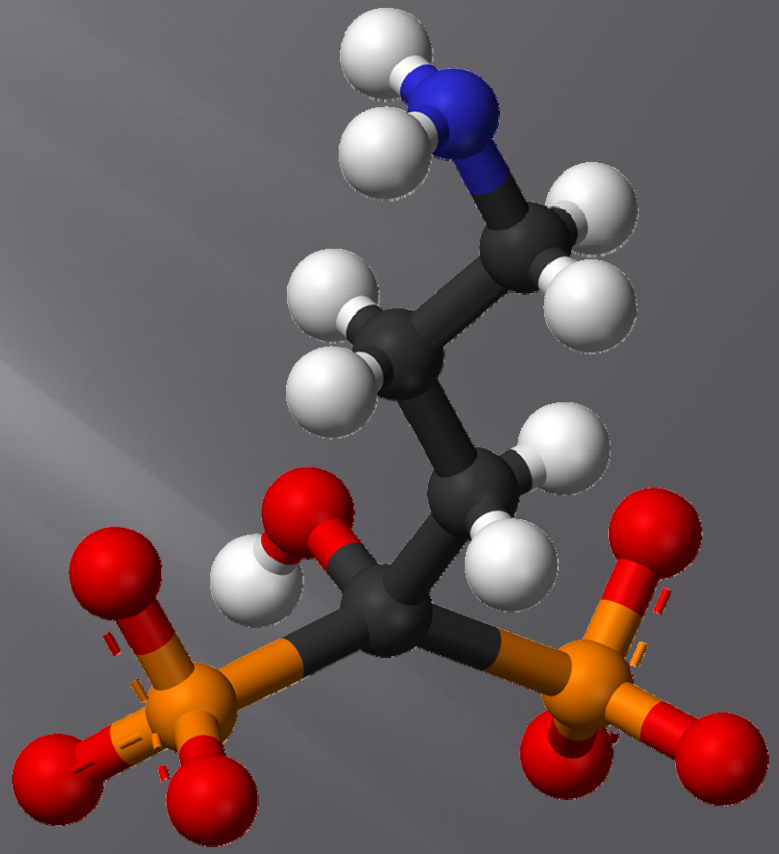
Study Course

- Women in the cohort were followed up until the first subtrochateric or femoral shaft fracture, death, or the end of the study period (March 31, 2009)



Exposure assessment

- Long term users: over 5 years of therapy
- Intermediate Users: 3-5 years of therapy
- Short term users (100 days to 3 years)
- Reference group of transient (<100 days in total users)



3D chemical model of Alendronate

Statistical Analysis

- The primary analysis examined the relationship between hospitalization for subtrochanteric femoral shaft fracture and cumulative duration of bisphosphonate use for more than 5 years.

- The secondary analysis tested the specificity of design and analysis by exploring the association between bisphosphonate use and typical osteoporotic femoral neck fracture or intratrochanteric neck fractures.

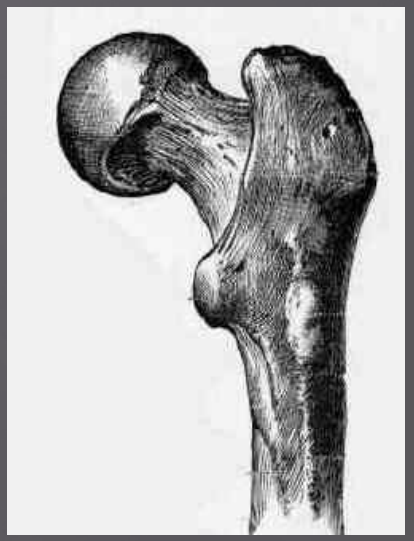
Results

- Over the 7-year study period, the study identified 205 466 women aged 68 years or older treated with a bisphosphonate who met the inclusion criteria.

- Within this group,the study identified 716 women (0.35%) who sustained a subtrochanteric or femoral shaft fracture following initiation of bisphosphonate therapy.

Results (continued)

- In the primary analysis, use of bisphosphonates for 5 years or longer was associated with an increased risk of hospitalization for subtrochanteric or femoral shaft fracture compared with transient use of bisphosphonates



- Shorter durations of bisphosphonate use were not associated with a statistically significant increase in the risk of subtrochanteric or femoral shaft fracture

Secondary analysis

- In the secondary analysis examining

the risk of typical osteoporotic fractures, the study identified 9723 women with fractures of the femoral neck or intertrochanteric region during bisphosphonate therapy.

- As expected, the study found that extended

bisphosphonate use (5 years) was associated with a reduced risk of typical fractures compared with transient use.

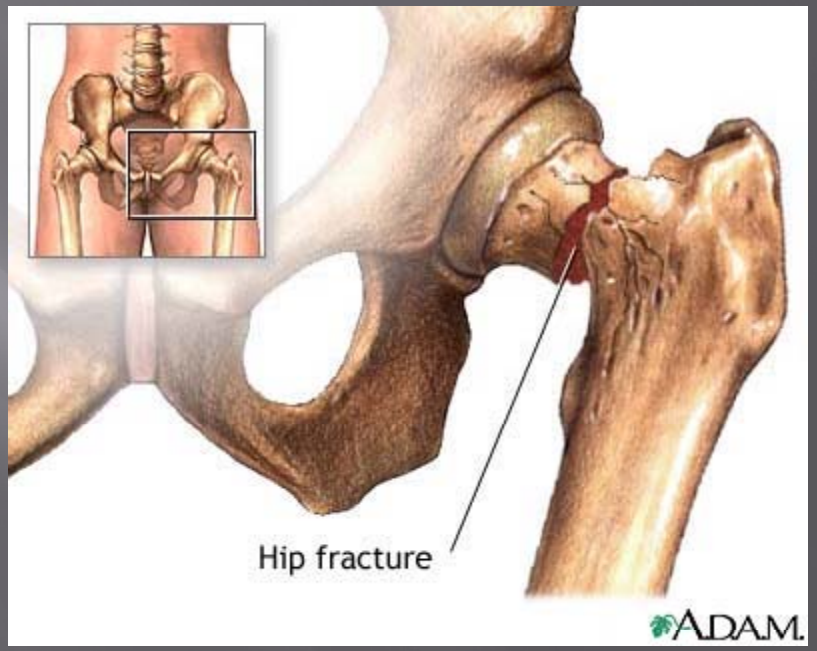
Conclusions

This population-based study found that long-term bisphosphonate treatment was associated with an increased risk of subtrochanteric or femoral shaft fracture in older women.

The increase in risk of subtrochanteric or femoral shaft fracture was apparent with 5 or more years of cumulative bisphosphonate drug exposure.

Conclusions Continued

As expected, extended bisphosphonate therapy was associated with a reduced risk of typical osteoporotic fractures



Recommendations

- Prolonged bisphosphonate use is associated with increased risk of subtrochanteric and femoral shaft fractures, although the absolute risk of such fractures is low.

- Bisphosphonates have demonstrated benefits in preventing the much more common typical fractures of osteoporosis, and this study should not deter clinicians from using them.