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*** Question 1. (20 points)**

PICO (**P**atient/**P**opulation **& P**roblem | **I**ntervention/Exposure | **C**omparison | **O**utcome). Please enter your Clinical Question (in sentence format) and its **P-I-C-O** elements below.

NOTE:

- For the purpose of this assignment, please ask a clinical question concerning treatment or preventive therapy. The critical analysis in section four is only relevant for this type of question.
- Questions relating to disease screening or the comparison of diagnostic tests are not acceptable.

Clinical Question (in sentence format)

In post-menopausal women at risk for diminishing bone density and fractures, is Vitamin D and Calcium supplementation effective in reducing fracture risk?

Patient/Population & Problem

Post-menopausal women at risk for diminishing bone density and fractures

Intervention/Exposure

Calcium and Vitamin D supplementation

Comparison

no supplementation

Outcome

Bone density and incidence of osteoporotic bone fractures

*** Question 2. (30 points)**

Databases This section will be graded partially on how well your search strategies match the concepts in your Clinical Question (PICO). For each database below:

- Copy and paste one or two of the most relevant results. *If no relevant results are obtained from a particular database, state this clearly and describe the search strategy that you used*.
- For PubMed searches, copy and paste your search strategy from the "History" section below the Advanced Search Builder on the "Advanced" PubMed web page **(see example)**. Review the PubMed Tutorials.
- Briefly discuss your search strategy and the number of results retrieved.

UpToDate (EBM synopses)

My exact search was "Calcium and Vitamin D for fractures in postmenopausal women" in UpToDate, yielding >20 articles including two relevant articles titled "Calcium and Vitamin D supplementation in osteoporosis" and "Overview of the management of osteoporosis in postmenopausal women."

Other articles discussed Vitamin D deficiency states, calcium homeostasis and management of osteoporosis.

PubMed (Clinical Queries - under PubMed Tools)

Search strategy in PubMed Clinical Queries (search history copied from the Advanced Search page):

(Therapy/Narrow[filter]) AND ((menopause OR postmenopausal OR postmenopause) AND fractures AND (bone density OR osteoporosis) AND vitamin D AND calcium) Sort by: PublicationDate Filters: published in the last 10 years; English
Results: 58

Relevant results included:

Calcium and vitamin d supplementation in postmenopausal women.
Aloia JF, Dhaliwal R, Shieh A, Mikhail M, Islam S, Yeh JK.
J Clin Endocrinol Metab. 2013 Nov;98(11):E1702-9. doi: 10.1210/jc.2013-2121. Epub 2013 Sep 24.
PMID: 24064695

Salovaara K, Tuppurainen M, Kärkkäinen M, Rikkonen T, Sandini L, Sirola J,

Honkanen R, Alhava E, Kröger H. Effect of vitamin D(3) and calcium on fracture risk in 65- to 71-year-old women: a population-based 3-year randomized, controlled trial--the OSTPRE-FPS. J Bone Miner Res. 2010 Jul;25(7):1487-95. doi: 10.1002/jbmr.48. PubMed PMID: 20200964.

Prentice RL, Pettinger MB, Jackson RD, Wactawski-Wende J, Lacroix AZ, Anderson
GL, Chlebowski RT, Manson JE, Van Horn L, Vitolins MZ, Datta M, LeBlanc ES, Cauley JA, Rossouw JE. Health risks and benefits from calcium and vitamin D supplementation: Women's Health Initiative clinical trial and cohort study. Osteoporos Int. 2013 Feb;24(2):567-80. doi: 10.1007/s00198-012-2224-2. Epub 2012 Dec 4. PubMed PMID: 23208074; PubMed Central PMCID: PMC3557387.

Cochrane Library (systematic reviews)

Search strategy copied from the Advanced Search:

There are 5 results from 10011 records for your search on 'menopause OR postmenopausal OR postmenopause in Title, Abstract, Keywords and vitamin d AND calcium in Title, Abstract, Keywords and fractures OR bone density OR osteoporosis in Title, Abstract, Keywords in Cochrane Reviews'

I decided to use the terms "fractures, bone density, and osteoporosis as synonyms here connected with "OR" since Cochrane is a much smaller database than PubMed.

The most relevant result in the Cochrane Reviews section was:

Vitamin D with or without calcium for treating osteoporosis in postmenopausal women
Emmanuel Papadimitropoulos , Beverley Shea , George A Wells , Peter Tugwell , Ann Cranney , William J Gillespie , R Josse , P Coyte and Greenwood
Online Publication Date: October 1997

However, this is a Protocol and not a complete review, It is also not current (1997).

The next most relevant result in this section was:

Vitamin D and vitamin D analogues for preventing fractures in post-menopausal women and older men
Alison Avenell , Jenson CS Mak and Dianne O'Connell
Online Publication Date: April 2014

The study selection criteria for this review were "Randomised or quasi-randomised trials that compared vitamin D or related compounds, alone or with calcium, against

placebo, no intervention or calcium alone, and that reported fracture outcomes in older people. The primary outcome was hip fracture."

In the "Other Reviews" section, this result seemed to be the most relevant:

Need for additional calcium to reduce the risk of hip fracture with vitamin D supplementation: evidence from a comparative metaanalysis of randomized controlled trials (Provisional abstract)
Centre for Reviews and Dissemination
Original Author(s): Boonen S , Lips P , Bouillon R , Bischoff-Ferrari H A , Vanderschueren D and Haentjens P
Journal of Clinical Endocrinology and Metabolism, 2007, 92(4), 1415-1423

National Guideline Clearinghouse (clinical practice guidelines)

My search was

1-17 of 17 results for
"postmenopausal and calcium and vitamin d"

(copied from the top of the search results page) and there were several relevant guidelines, including:

Guideline Summary NGC:009627 2013 Feb 26
Vitamin D and calcium supplementation to prevent fractures in adults: U.S. Preventive Services Task Force recommendation statement.
U.S. Preventive Services Task Force

Guideline Summary NGC:009312 2004 Jan (revised 2012 Sep)
Osteoporosis.
American College of Obstetricians and Gynecologists

*** Question 3. (10 points)**

Therapy Article Selected for Critical Appraisal from PubMed Clinical Queries. Please enter the complete citation ***including PMID AND the abstract*** for the reference you select **(see example)**. The choice of article will be graded according to its relevancy to the elements of the Clinical Question (PICO) and therapy study type.

J Bone Miner Res. 2010 Jul;25(7):1487-95. doi: 10.1002/jbmr.48.
Effect of vitamin D(3) and calcium on fracture risk in 65- to 71-year-old women: a population-based 3-year randomized, controlled trial--the OSTPRE-FPS.
Salovaara K(1), Tuppurainen M, Kärkkäinen M, Rikkonen T, Sandini L, Sirola J, Honkanen R, Alhava E, Kröger H.

Author information:
(1)Bone and Cartilage Research Unit, Clinical Research Centre, University of Kuopio, Kuopio, Finland. kari.salovaara@kuh.fi
Comment in
J Bone Miner Res. 2010 Dec;25(12):2801; author reply 2802.

Antifracture efficacy of high-dose vitamin D (800 IU) and calcium (1000 mg) remains controversial. To determine whether daily 800 IU of vitamin D and 1000 mg of calcium supplementation prevents fractures, we randomized 3432 women of the population-based Osteoporosis Risk Factor and Prevention (OSTPRE) Study cohort (ages 65 to 71 years) living in the region of northern Savonia, Finland (latitude 62 degrees to 64 degrees N) for 3 years to receive 800 IU of cholecalciferol and 1000 mg of calcium as calcium carbonate or to a control group that did not receive placebo. The main outcome measure was incident fractures. Fracture data were collected in telephone interviews and validated. Data on 3195 women, 1586 in the intervention group and 1609 in the control group, were available for analysis. In adjusted Cox proportional hazards models, the risk of any fracture decreased in the vitamin D and calcium group by 17% [adjusted hazard ratio (aHR) = 0.83; 95% confidence interval (CI) 0.61-1.12], and the risk of any nonvertebral fracture decreased by 13% (aHR = 0.87; 95% CI 0.63-1.19). The risk of distal forearm fractures decreased by 30% (aHR = 0.70; 95% CI 0.41-1.20), and the risk of any upper extremity fractures decreased by 25% (aHR = 0.75; 95% CI 0.49-1.16), whereas the risk of lower extremity fractures remained essentially equal (aHR = 1.02; 95% CI 0.58-1.80). None of these effects reached statistical significance. In conclusion, this study did not produce statistically significant evidence that vitamin D and calcium supplementation prevents fractures in a 65- to 71-year-old general population of postmenopausal women.

PMID: 20200964 [PubMed - indexed for MEDLINE]

*** Question 4. (40 points)**

Critical Appraisal of Therapy or Prevention Article: for the article you have selected, answer questions 1-11 below.

* Print or copy the article you chose to analyze and give it to David Morohashi, MD.*

1. Was the assignment of patients to treatment randomized?

(●) Yes ( ) No ( ) Can't Tell

2. Were all the patients who entered the trial properly accounted for and attributed at its conclusion?

(●) Yes ( ) No ( ) Can't Tell

- Was patient follow-up complete?

  (●) Yes ( ) No ( ) Can't Tell

- Were patients analyzed in the groups to which they were randomized (intention to treat analysis)?

  (●) Yes ( ) No ( ) Can't Tell

3. Were patients, their clinicians, and study personnel 'blind' to treatment?

( ) Yes (●) No ( ) Can't Tell

4. Were the groups similar at the start of the trial?

(●) Yes ( ) No ( ) Can't Tell

- Were baseline prognostic factors (demographics, co-morbidity, disease severity, other known confounders) balanced?

  ( ) Yes (●) No ( ) Can't Tell

- If the baseline prognostic factors were different, were they adjusted for?

  (●) Yes ( ) No ( ) Can't Tell

5. Aside from the experimental intervention, were the groups treated equally?

(●) Yes ( ) No ( ) Can't Tell

- Was there co-intervention in the intervention?

  ( ) Yes (●) No ( ) Can't Tell

- Was there contamination of the groups?

Yes ○ No ● Can't Tell

- Was there compliance?

  Yes ● No ○ Can't Tell

6. Overall, are the results of the study valid?

Yes ● No ○ Can't Tell

Tools You Can Use Online

- Statistics Calculations: interpreting the importance and precision of therapeutic results
  http://www.ebm.med.ualberta.ca/TherapyCalc.html
- EBM Calculators
  http://ebm-tools.knowledgetranslation.net/calculator
- RLO: numbers needed to treat (NNT) and numbers needed to harm (NNH)
  http://www.nottingham.ac.uk/nmp/sonet/rlos/ebp/nnt_nnh/
- See 'Additional Resources for Critical Appraisal'
  Family Medicine Clerkship

7. How large was the treatment effect?

- Absolute risk reduction? Describe:

  Regarding each individual's risk of having greater or equal to 1 under the given intervention: given that recurrance rate in the intervention group was 78/1586 and in the control group was 92/1609, Absolute Risk Reduction = 0.0092 (or 0.92%)

- Relative risk reduction? Describe:

  Regarding each individual's risk of having greater or equal to 1 fracture under the given intervention: Relative Risk Reduction = Absolute risk reduction/incidence among controls = 0.16 (or 16%). This indicates that compared to the control group, risk of recurrance during the study period while in the intervention group was lower by 16%.

8. How precise was the estimate of the treatment effect?

- Confidence intervals? Describe:

  The 95% confidence interval for the given relative risk (which allows for calculation of the standard error of relative risk), with z = 1.96 = 0.63 to 1.13. Statistically, the precision of the estimate of treatment effect leaves significant room for improvement. While the finding may be enhanced by increasing power, it is still statistically unproven whether there is a difference made by the intervention.

9. Can the results be applied to my patient care?

Describe why or why not:

While conducted in a Scandinavian country, given the findings in this study, I believe this is applicable to my patient care in the case of a woman who is post-menopausal in her 60s and of average socioeconomic class here in the US, concerned about fracture risk. In the similarly developed country, I believe the demographics, severity, co-morbidity and other prognostic factors are similar to my patients. Considerations such as availability of similar medical resources and Hormone Replacement Therapy and accounting for similar concerns as my patient population such as alcohol use, smoking, and endocrinopathies (DM1, Hyperthyroidism) were addressed and balanced in the study. There was a narrow age group (65-71yo) that was followed in this study, and further societal influences such as baseline Vitamin D and Calcium intake via fortified milk and education were taken into consideration, and I believe similar to practices in the US. The effect size was calculated for different fracture types separately and adjusted for age, BMI, smoking, alcohol use, previous fracture, parental hip fracture, gluocorticoid use, diagnosed RA, secondary osteoporosis, which are all validated confounders of fracture risk estimation. Further, the subgroup that had closer follow-up care showed no confounding impact on the larger data set.

- Are the patients similar for demographics, severity, co-morbidity, and other prognostic factors as my patient?

  (●) Yes ( ) No ( ) Can't Tell

- Is there a compelling reason why the results should not be applied? Describe:

  While further studies with higher power would assist in further identifying benefit or lack thereof, there is no compelling reason why the results in this study would not be applied to the care of my patients.

10. Were all the clinically important outcomes considered?

(●) Yes ( ) No ( ) Can't Tell

- What are they? Describe:

  My outcome in my initial clinical question included incidence of bone fractures, which was well addressed in this study. Further, the fractures were sub-classified by location (vertebral, nonvertebral, upper extremity, lower extremity) and whether they would be considered osteoporotic, which were beneficial considerations. The study further addressed 25-hydroxy-VitD levels, which are relevant to the individual impact of the Vitamin D component in addition to the Calcium on the outcomes. One outcome that was not specifically addressed which may be relevant was bone mineral density, which underlies the WHO's diagnostic criteria for osteoporosis. However, I believe the study adequately addressed the appropriate clinically important outcomes.

- Are the substitute endpoints (also known as surrogates) valid?

  (●) Yes ( ) No ( ) Can't Tell

11. Are the likely treatment benefits worth the potential harms and costs?

(●) Yes ( ) No ( ) Can't Tell

- Why? Describe:

  The results of this study showed that there was no statistically significant reduction of bone fractures of any type or stratification (osteoporotic (calculated RR: 0.18, CI: 0.55 - 1.22) or otherwise) among 65-71 year old post-menopausal women who were given free Calcium and Vitamin D supplements at high doses (800IU Vitamin D and 1000mg Calcium daily). There was minimal dropout due to adverse effects, with GI upset, nausea and skin reactions being the top 3 adverse reactions in the intervention group leading to discontinuation of the intervention. This and the relatively low cost of Calcium and Vitamin D supplements, leads me to believe that the potential harms are low. The authors admit that the study was powered to detect a 30% decrease in fracture rate with expected incidence of 30/1000/yr. However, when the studied only yielded a fracture incidence of 18/1000/yr, the benefit was not found to be statistically significant. Thus, the benefit may have been masked due to insufficient power. Overall, at this point, the benefits are unconfirmed while the harms and costs are low, so I would recommend not stopping the supplement if the patients perceive a benefit, but advising patients of the lack of statistical significant evidence suggesting benefit in reducing fracture risk from this study.