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Iuliano S, Poon S, Robbins J, et al. Effect of dietary sources of calcium and protein on hip fractures and falls in older adults in residential care: cluster randomised controlled trial. BMJ. 2021;375:n2364.

What We Know, Think We Know, or Are Starting to Know

Them bones them bones need calcium. Or do they? This is one of the most debated subjects in nutrition, and it brings together several challenges for nutrition research:

1. Are randomised controlled trials influenced by baseline nutritional status?
2. Do we understand what levels of intake represent true insufficiency and adequacy?
3. Is the potential effect of the nutrient modified by other dietary and lifestyle factors?
4. Is there a difference between the nutrient as supplement and nutrient from food?

The research on calcium and bone health throws all of this at us. For example, in relation to No.1 above, the Women's Health Initiative found no effect of 1,000mg calcium and 400IU vitamin D per day on risk of fractures over 7yrs [(1)].

But not so fast: both the placebo group and the intervention group had an average daily baseline calcium intake of ~1,1150mg. So, the real comparison was "more of enough vs. more than enough", not 'calcium vs. placebo'. If you haven't watched the Research Lecture on this issue of nutrients and RCTs, here is the link.

What about No.2? Calcium recommendations have typically been based on calcium balance studies, i.e., looking at when calcium losses are matched by calcium intake. Depending on the analytical approach taken, focusing on calcium balance as a determinant of adequate calcium requirements may result in ranges of anywhere from 500mg/d to 1,500mg/d [(2,3)].

But hold on: when has nutrient balance been a good marker for optimal intakes? Think about dietary protein: the recommended daily intake is based on the minimum amount needed to maintain positive nitrogen [protein] balance, but this is far from optimal for people who are athletic, older, pregnant, etc.

No.3 is something we certainly know in relation to calcium, that both vitamin D and dietary protein act as strong moderating factors in the associations between calcium and bone health [(4,5)]. Finally, what of No.4? There is evidence that dietary calcium is associated with more favourable bone mineral density in postmenopausal women compared to women obtaining calcium through supplements [(6)].

All of this leads us to the present study.

The Study

The present study was conducted as a cluster randomised* controlled trial in permanent residents of residential care homes for the elderly in Australia. 30 care homes were randomly assigned to the intervention, and 30 to the control.

The study deliberately had an inclusion criteria of care homes that served no more than two servings of dairy a day, i.e., likely to have daily calcium intakes of <600mg/d.

The intervention targeted achieved daily calcium intake of 1,300mg and 1g per kilogram bodyweight of dietary protein from increased dairy foods specifically. A serving of dairy was defined as 250ml milk, 200g yogurt, or 40g cheese. The control care homes maintained their usual menus.

The primary outcome was time to a fracture occurring. Secondary outcomes included time to falls, changes in bone morphology, and biochemical indicators of nutrient status and bone turnover. The total duration of the intervention was 2yrs.

*Geek Box: Cluster Randomisation

The present study had a design that is slightly different to the traditional method of randomisation, using a cluster-randomisation method. What does "cluster" mean in this context? It means that the unit of randomisation is not an individual. Rather, a cluster of individuals in a pre-specified group are randomised together. This method of randomisation is often used in education and public health policy research. For example, suppose you want to do an intervention in a school comparing the effects of a reading technique in children. If you randomised individuals in a classroom, you could have a situation where a child receiving the intervention is sitting next to a child in the control group; this would lead to what is called "contamination", i.e., the potential for the treatment and control groups to mix and thus compromise the intervention. To prevent contamination, and also for ease of implementation, it would be more useful to randomise the entire class; therefore, randomisation assigns the whole of Class A to the intervention and Class B is assigned to the control. Thus, the class is the "cluster". In the present study, the residential care home was the unit of randomisation.

Results: 54 care homes completed the intervention, 27 in the intervention and 29 in the control. The total sample size of individual participants was 3,301 [70% female] in the intervention group and 3,894 [67% female] in the control group. Average age at baseline with 86yrs in all participants.

Dairy foods intake increased from an average of 2 servings to 3.5 servings per day. This reflected equivalent intakes to 250ml milk, 20g cheese, and 100g yogurt, providing 562mg/d additional calcium and 12g/d protein. Thus, achieved daily calcium was 1,142mg/d and achieved protein was 1.1g/kg.

- ***Risk of Fractures*:** Over an average of 12.6 months follow-up, there were 121 fractures in the intervention arm and 203 in the control arm. Compared to the control arm, the intervention arm had a 33% [HR 0.67, 95% CI 0.48 to 0.93) lower risk of overall fracture. The risk of hip fracture was 46% [HR 0.54, 95% CI 0.35 to 0.83] in the intervention arm. The difference in risk of fractures became significant at 5-months into the intervention.

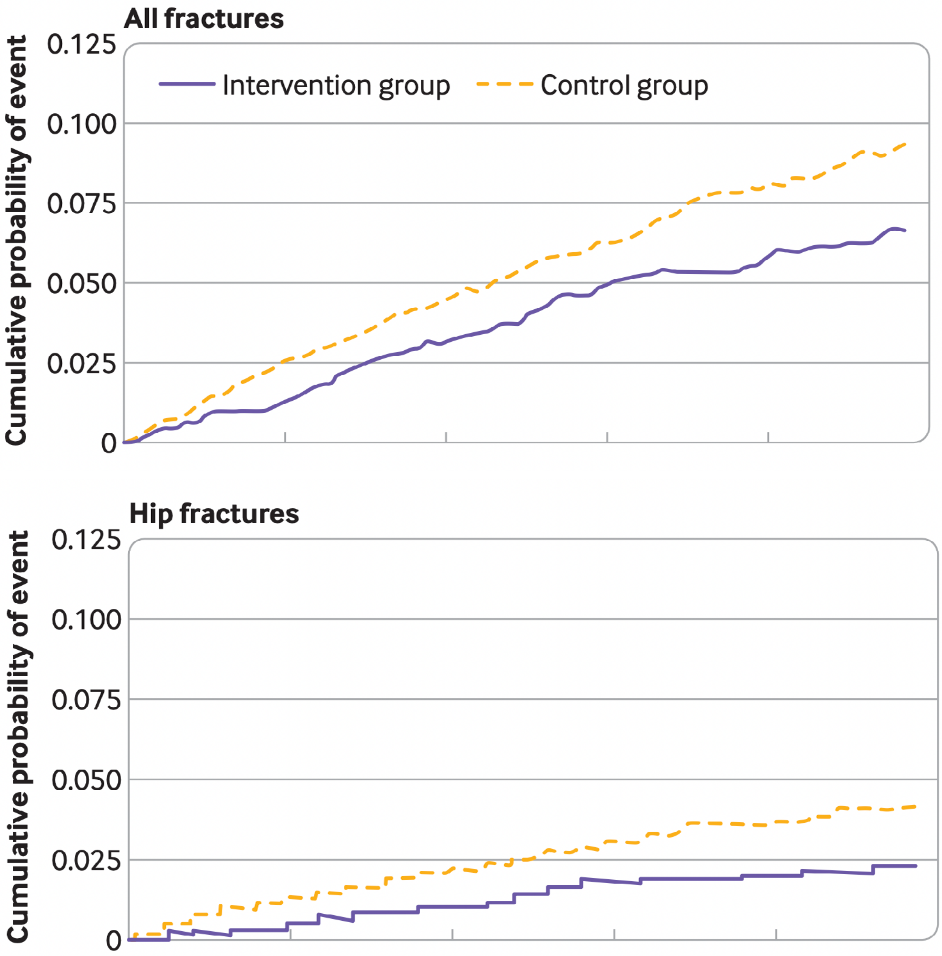

***Figure** from the paper illustrating [**top**] the probability of all fractures between the intervention arm [**solid line**] and control arm [**dashed line**], and [**bottom**] the probability of hip*

- ***Risk of Falls*:** Compared to the control arm, there was an 11% [HR 0.89, 95% CI 0.78 to 0.98] lower risk of falls in the intervention arm. All except one fracture recorded in the study were the result of a fall. The difference in risk of falls became significant at 3-months into the intervention.

- ***Risk of Mortality*:** There was no significant difference in mortality risk between groups, 27% of the intervention arm died during the study compared to 28% of the control arm.

The Critical Breakdown

Pros: The study utilised a block and stratified randomisation procedure to maintain similarities between care homes and and geographic area. Participants remained blinded to the intervention, or where changes to diet were obvious [cheese served instead of biscuits], blind to the purpose of the change. The investigators targeted populations with low levels of the exposure of interest, i.e., calcium and protein. It's hard to state what a huge 'Pro' this is for a nutrition intervention: deliberately targeting participants with likely inadequate, or at least suboptimal, levels of intake mean more likelihood of detection 'true' effects of the nutrients of interest. Vitamin D was held constant throughout the trial [baseline levels were 72nmol/L, more than adequate], so adults had sufficient vitamin D but insufficient protein and calcium. A dietitian was provided to each intervention facility to assist food service staff in delivering the intervention foods.

Cons: Obviously the study targeted a particular population, but it was also surprising that the average age was 86. This was a population with substantial comorbidity, with 66% of participants in both groups at risk of malnourishment, 52% with cognitive impairment, and 65% with cardiovascular disease. This is all not a negative *per se*, just a caveat regarding wider potential application. Diet was assessed in a small subgroup of the total study population, although the authors state this is likely to be representative of the care home diets. Biochemical indicators of bone morphology and bone turnover were also only assessed in small subgroup of the participants, which lacked statistical power to detect differences between the intervention arm and control arm.

Key Characteristic

The setting of this trial is the key characteristic of the intervention. Why? Because differences have been observed in the diet and bone health literature between setting: in the community vs. residential care homes. This difference is a modifying lifestyle factor.

In a trial of >3,000 women over 70yrs of age, Porthouse et al. found no evidence that 1,000mg calcium + 800IU vitamin D_3 per day reduced risk of fractures or falling incidence [7]. In the RECORD trial, there was also no difference in fracture rates in the over 70yrs participants using 1,000mg calcium, 800IU vitamin D_3, a combination of both, or a placebo [8].

The participants in those trials were, however, drawn from the community. In the context of RCT's based in residential care homes, 1,200mg calcium and 800IU vitamin D_3 has consistently resulted in reduced risk of fractures in subjects over 70 years [9,10]. These positive outcomes may reflect low baseline calcium intakes and vitamin D deficiency common in residential care home settings [9,10].

Interesting Finding

The interesting finding of this study is the primary outcome, but in a specific context: vitamin D repletion in the entire study cohort. One of the issues in teasing out effects of calcium on bone health is that calcium is mostly supplemented alongside varying doses of vitamin D_3 [4]. Indeed, previous research has shown that positive effects of vitamin D supplementation are only observed when calcium is supplemented alongside vitamin D [4].

This interaction is often used to suggest that there is no effect of calcium alone. However, participants in these studies often have insufficient vitamin D levels, which is important as the relationship between risk of fractures and blood levels of vitamin D [i.e., 25(OH)D levels] is primarily observed below levels of 70nmol/L [11]. This range of 25(OH)D levels is also the range at which maximal intestinal absorption of calcium is observed [12].

Generally, the benefit to the modifying effect of vitamin D on calcium is that vitamin D up-regulates calcium absorption, allowing for a lower threshold of dietary calcium intake. However, what happens when vitamin D is sufficient, but calcium low? The present study addressed that question. By maintaining vitamin D constant and having blood levels of 25(OH)D at which we would: a) expect to see maximal effects of vitamin D on bone health, and; b) expect to see maximal intestinal calcium absorption, the present study provides evidence of independent effects of calcium and protein that have been previously been difficult to determine.

Relevance

In elderly populations over 65 years, high incidence of osteoporotic fractures is a major public health concern due to correlations with higher mortality and morbidity, and decreased quality of life [13].

Calcium and vitamin D are the most important nutrients for bone health in this population, yet 25(OH)D levels are commonly deficient and population-wide dietary surveys estimate calcium intake in the elderly at 3-600mg per day in women and 350-700mg in men, short of the EU RDA of 7-800mg [13]. The effect of higher doses of vitamin D_3 may relate to the magnitude of increasing 25(OH)D levels from <25nmol/L to achieved levels of ~70nmol/L [11].

As discussed under ***Interesting Finding***, above, the design of this study and control of 25(OH)D levels points to a direct effect of the increase in calcium and protein achieved by the intervention. It is important to note that we can't necessarily say whether calcium or protein contributed more, but this is largely a moot point for nutritional exposures given the intercorrelated nature of whole-foods and diet. This interaction has been shown before; in an analysis of the Women's Health Initiative, Dawson-Hughes et al. showed that participants in the calcium + vitamin D supplement group with the highest dietary protein intake had the most significant effects on bone mineral density [5].

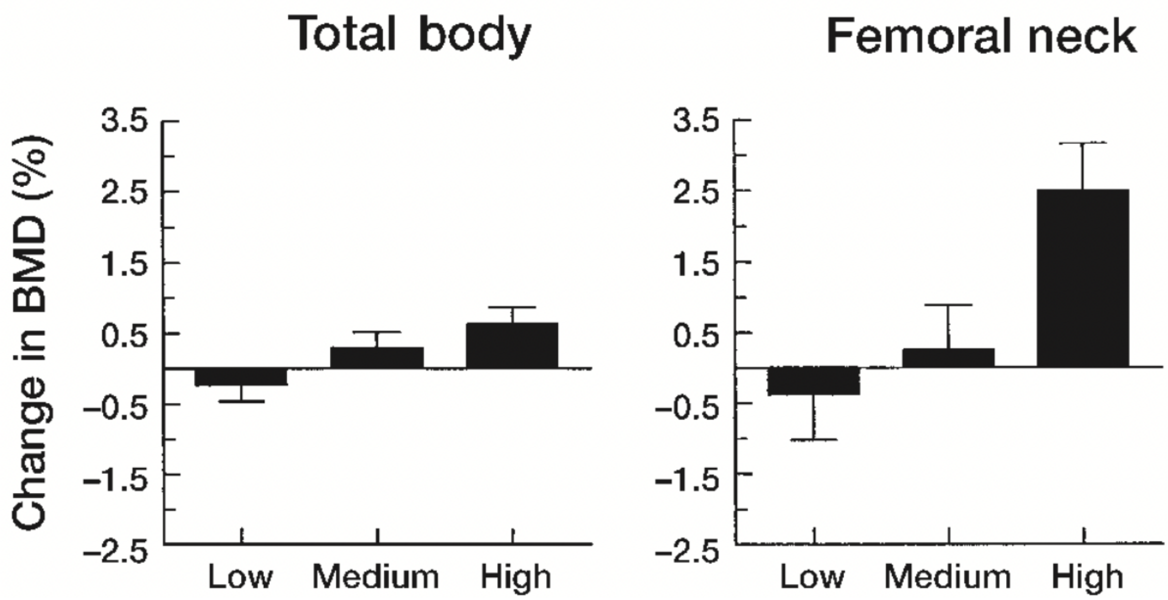

Figure (R) illustrating the effect of tertiles of dietary protein intake - low, medium, and high - on total body bone mineral density [left] and femoral neck bone mineral density [right] in participants supplementing 1,000mg calcium and 400IU vitamin D per day. As can clearly be seen in both graphs, those with the highest dietary protein had the greatest positive effect, highlighting the modifying effect of dietary protein in relation to calcium and vitamin D.

By holding vitamin D constant in the present study, it is the interaction of dietary protein and calcium that becomes interesting. Previous research has shown that diets with <0.8g/kg dietary protein increase calcium losses [14]. The achieved levels of 1.1g/kg in the present study thus appear to be an important factor, while the interaction with achieved dietary calcium builds on prior research to suggest the combination of these nutrients may have additive effects on bone health.

Application to Practice

The context of the very elderly population with substantial comorbidity in this study is important to consider. However, the findings provide additional context to an ongoing area of debate. First, this was a food-based intervention and therefore has more immediate wider application. Second, vitamin D was held constant throughout the trial, and this points to a real effect of the additional calcium and protein provided by the additional dairy foods [while acknowledging that the food matrix may also play a role with other beneficial nutrients, like phosphorous]. Finally, the levels of intake - 250ml milk, 20-40g cheese, 100-200g yogurt - are readily achievable for the elderly. Given the low levels of calcium and protein common even in the >65yrs age group, this study likely has important application to a wider elderly demographic.

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