Calcium intake and bone mineral density: systematic review and meta-analysis

Vicky Tai,[1] William Leung,[2] Andrew Grey,[1] Ian R Reid,[1] Mark J Bolland[1]

EDITORIAL by Michaëlsson
RESEARCH, p 12

[1]Department of Medicine, University of Auckland, Private Bag 92019, Auckland 1142, New Zealand
[2]Department of Public Health, University of Otago, PO Box 7343, Wellington 6242, New Zealand
Correspondence to: M Bolland
m.bolland@auckland.ac.nz

Cite this as: *BMJ* 2015;351:h4183
doi: 10.1136/bmj.h4183

This is a summary of a paper that was published on thebmj.com as *BMJ* 2015;351:h4183

thebmj.com

- Overdiagnosis of bone fragility in the quest to prevent hip fracture (*BMJ* 2015; 350: h2088)
- Calcium supplements with or without vitamin D and risk of cardiovascular events (*BMJ* 2011; 342: d2040)
- Effect of calcium supplements on risk of myocardial infarction and cardiovascular events (*BMJ* 2010; 341: c3691)

STUDY QUESTION

Does increasing calcium intake from dietary sources have any effects on bone mineral density and, if it does, are they similar to the effects of calcium supplements?

SUMMARY ANSWER

Increasing calcium intake, whether from dietary sources or by taking calcium supplements, leads to small (1-2%) non-progressive increases in bone density, without any ongoing reduction in rates of loss of bone density beyond one year.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Recent concerns about the safety of calcium supplements have led to recommendations to increase calcium intake through food rather than by taking supplements, but the effect of this on bone health is not known. In this meta-analysis of 59 randomised controlled trials, increases in calcium intake, either by dietary sources or supplements, had small non-progressive effects on bone density that are unlikely to translate into clinically meaningful reductions in fractures.

Selection criteria for studies

We searched Ovid Medline, Embase, Pubmed, and relevant systematic reviews for randomised controlled trials of dietary sources of calcium or calcium supplements (with or without vitamin D) in participants aged 50 or older with bone density as an outcome. Data were pooled with random effects meta-analyses.

Primary outcomes

The primary endpoints were the percentage changes in bone density from baseline at the lumbar spine, femoral neck, total hip, forearm, and total body.

Main results and role of chance

In 15 randomised controlled trials, increasing calcium intake from dietary sources increased bone density by 0.6-1.0% at the skeletal sites total hip and total body at one year and by 0.7-1.8% at these sites and the lumbar spine and femoral neck at two years. There was no effect on bone density at the forearm. In 51 randomised controlled trials, calcium supplements increased bone density by 0.7-1.4% at all five skeletal sites at one year, by 0.8-1.5% at two years, and by 0.8-1.8% at more than two and a half years (range of duration of trials 3-5 years).

Pooled analyses of trials of dietary sources of calcium and calcium supplements

Time point	No of trials	Difference in % change in bone density at lumbar spine from baseline (95% CI)
Trials of dietary sources of calcium		
1 year	11	0.6 (–0.1 to 1.3)
2 years	8	0.7 (0.3 to 1.2)
Calcium supplement trials		
1 year	27	1.2 (0.8 to 1.7)
2 years	21	1.1 (0.7 to 1.6)
>2.5 years	8	1.0 (0.3 to 1.6)

Bias, confounding, and other reasons for caution

Bone density is only a surrogate for the clinical outcome of fracture, but the results align with existing evidence that calcium supplements have small inconsistent effects on the risk of fracture. In about 60% of the meta-analyses, statistical heterogeneity between the studies was high (I^2>50%), indicating substantial variability in the results of trials included in these analyses. Subgroup analyses generally did not substantially reduce or explain the heterogeneity.

Study funding/potential competing interests

The study was funded by the Health Research Council (HRC) of New Zealand. MJB is the recipient of a Sir Charles Hercus health research fellowship. IRR has received research grants and honorariums from Merck, Amgen, Lilly, and Novartis.

Calcium intake and risk of fracture: systematic review

Mark J Bolland,[1] William Leung,[2] Vicky Tai,[1] Sonja Bastin,[3] Greg D Gamble,[1] Andrew Grey,[1] Ian R Reid[1]

EDITORIAL by Michaëlsson
RESEARCH, p 11

[1]Department of Medicine, University of Auckland, Private Bag 92019, Auckland 1142, New Zealand
[2]Department of Public Health, University of Otago, PO Box 7343, Wellington 6242, New Zealand
[3]Department of Radiology, Starship Hospital, Private Bag 92024, Auckland 1142, New Zealand
Correspondence to: M Bolland
m.bolland@auckland.ac.nz

Cite this as: *BMJ* 2015;351:h4580
doi: 10.1136/bmj.h4580

This is a summary of a paper that was published on thebmj.com as *BMJ* 2015;351:h4580

thebmj.com

- Overdiagnosis of bone fragility in the quest to prevent hip fracture (*BMJ* 2015; 350: h2088)
- Calcium supplements with or without vitamin D and risk of cardiovascular events (*BMJ* 2011; 342: d2040)
- Effect of calcium supplements on risk of myocardial infarction and cardiovascular events (*BMJ* 2010; 341: c3691)

STUDY QUESTION

Does increasing calcium intake prevent fractures and are there differences between the effects of dietary sources of calcium and calcium supplements on fracture prevention?

SUMMARY ANSWER

Dietary calcium intake is not associated with fracture risk, and there is no clinical trial evidence that increasing calcium intake from dietary sources prevents fractures, while evidence that calcium supplements prevent fractures is weak and inconsistent.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Recently, experts have recommended increasing calcium intake through diet rather than by taking supplements, but it is not known whether increasing dietary calcium intake prevents fractures. In this systematic review of randomised controlled trials and cohort studies, dietary calcium intake was not associated with fracture risk, there was no evidence that increasing calcium intake prevents fractures, and calcium supplements had only small inconsistent benefits on fracture prevention.

Selection criteria for studies

We searched Ovid Medline, Embase, PubMed, relevant systematic reviews, and recent reviews on fracture risk for randomised controlled trials and cohort studies of dietary sources of calcium or calcium supplements (with or without vitamin D) with fracture as an outcome in which participants were aged 50 or older. Data from randomised controlled studies were pooled with random effects meta-analyses.

Primary outcomes

The primary endpoints were the relative risks or hazard ratios for total, hip, vertebral, and forearm fracture.

Main results and role of chance

There were only two small eligible randomised controlled trials of dietary sources of calcium, but 44 eligible cohort studies. For dietary calcium, most studies reported no association between calcium intake and fracture (14/22 for total, 17/21 for hip, 7/8 for vertebral, and 5/7 for forearm fracture). For milk (25/28) and dairy intake (11/13), most studies also reported no associations. In 26 randomised controlled trials, calcium supplements reduced the risk of total fracture (relative risk 0.89, 95% confidence interval 0.81 to 0.96) and vertebral fracture (0.86, 0.74 to 1.00) but not hip (0.95, 0.76 to 1.18) or forearm fracture (0.96, 0.85 to 1.09). In four trials at lowest risk of bias, there was no effect on fracture risk at any site. Results were similar for trials of calcium monotherapy and co-administered calcium and vitamin D. Only one trial in frail elderly women in residential care with low dietary calcium intake and vitamin D concentrations showed significant reductions in fracture risk.

Bias, confounding, and other reasons for caution

There are no validated topic specific tools available to assess the risk of bias in the cohort studies, although generally observational studies are considered to be at higher risk of bias than large well conducted randomised controlled trials. We were unable to perform meta-analyses of observational data because of the different ways in which the data were reported. For the randomised controlled trials, most were considered to be at moderate or high risk of bias, and there was also evidence for publication bias.

Study funding/potential competing interests

The study was funded by the Health Research Council (HRC) of New Zealand, and MJB is the recipient of a Sir Charles Hercus Health Research Fellowship. IRR has received research grants and/or honorariums from Merck, Amgen, Lilly, and Novartis.

Results of studies of calcium intake or supplements and fracture

	Dietary calcium intake		Calcium supplements	
	No of cohort studies	Proportion with no association with fracture	No of randomised trials	Relative risk of fracture (95% CI)
Total fracture	22	64%	20	0.89 (0.81 to 0.96)
Hip fracture	21	81%	13	0.86 (0.74 to 1.00)
Vertebral fracture	8	88%	12	0.95 (0.76 to1.18)
Forearm fracture	7	71%	8	0.96 (0.85 to 1.09)

Use of HLA-B*58:01 genotyping to prevent allopurinol induced severe cutaneous adverse reactions in Taiwan: national prospective cohort study

Tai-Ming Ko,[1 2] Chang-Youh Tsai,[3 4] Shih-Yang Chen,[5] Kuo-Shu Chen,[6] Kuang-Hui Yu,[7] Chih-Sheng Chu,[8 9 10] Chung-Ming Huang,[2 11] Chrong-Reen Wang,[12] Chia-Tse Weng,[12] Chia-Li Yu,[13] Song-Chou Hsieh,[13] Jer-Chia Tsai,[8 9 10] Wen-Ter Lai,[8 9 10] Wen-Chan Tsai,[8 9 10] Guang-Dar Yin,[14] Tsan-Teng Ou,[8 9 10] Kai-Hung Cheng,[8 9 10] Jeng-Hsien Yen,[8 9 10] Teh-Ling Liou,[3] Tsung-Hsien Lin,[8] Der-Yuan Chen,[4 15 16] Pi-Jung Hsiao,[8 9 10] Meng-Yu Weng,[12] Yi-Ming Chen,[4 15 16] Chen-Hung Chen,[17] Ming-Fei Liu,[12] Hsueh-Wei Yen,[8 9 10] Jia-Jung Lee,[8] Mei-Chuan Kuo,[18] Chen-Ching Wu,[8 9 10] Shih-Yuan Hung,[19 20] Shue-Fen Luo,[7 21] Ya-Hui Yang,[22 23] Hui-Ping Chuang,[1] Yi-Chun Chou,[1] Hung-Ting Liao,[1] Chia-Wen Wang,[1] Chun-Lin Huang,[1] Chia-Shuo Chang,[1] Ming-Ta Michael Lee,[1 24] Pei Chen,[1] Chih-Shung Wong,[25 26] Chien-Hsiun Chen,[1 27] Jer-Yuarn Wu,[1 27] Yuan-Tsong Chen,[1 28] Chen-Yang Shen,[1 29 30] for the Taiwan Allopurinol-SCAR Consortium

EDITORIAL by Li-Wan-Po

Correspondence to: C-Y Shen
bmcys@ibms.sinica.edu.tw
Full author affiliations can be found in the version on thebmj.com

Cite this as: *BMJ* 2015;351:h4848
doi: 10.1136/bmj.h4848

This is a summary of a paper that was published on thebmj.com as *BMJ* 2015;351:h4848

STUDY QUESTION

Can screening for the HLA-B*58:01 allele before allopurinol treatment help prevent severe cutaneous adverse reactions (SCARs)?

SUMMARY ANSWER

Prospective screening of the HLA-B*58:01 allele, coupled with an alternative drug treatment for carriers, substantially decreased the incidence of allopurinol induced SCARs.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Strong associations between the HLA-B*58:01 allele and allopurinol induced SCARs has been found in a wide range of ethnic populations. This nationwide prospective study with an adequate sample size provides a strong basis for routine testing for this allele as well as for general implementation of personalised medicine testing.

Participants and setting

Patients who had an indication for allopurinol treatment but had not taken allopurinol previously were recruited from 15 participating hospitals throughout Taiwan.

Design, size, and duration

A prospective cohort study (n=2926) was performed from July 2009 to August 2014. DNA purified from 2910 participants' peripheral blood was used to assess the presence of HLA-B*58:01. Participants who tested positive were advised to avoid allopurinol and referred to an alternative drug treatment, or advised to continue with their prestudy treatment; those who tested negative were given allopurinol. Participants were interviewed once a week for two months to monitor symptoms.

Main results and the role of chance

The historical incidence of allopurinol induced SCARs, estimated by the National Health Insurance research database of Taiwan, was used for comparison. Mild, transient rash without blisters developed in 97 (3%) participants during follow-up. None of the participants was admitted to hospital owing to adverse drug reactions. SCARs did not develop in any of the participants receiving allopurinol who screened negative for HLA-B*58:01. By contrast, seven cases of SCARs were expected, based on the estimated historical incidence of allopurinol induced SCARs nationwide (0.30% per year, 95% confidence interval 0.28% to 0.31%; P=0.0026; two side one sample binomial test).

Bias, confounding, and other reasons for caution

For countries or populations in which the prevalence of HLA-B*58:01 is ill defined, further studies are needed to estimate the prevalence for possible application of this screening.

Generalisability to other populations

Our results suggest that in countries where the HLA-B*58:01 is relatively prevalent and where a tight association has been found, screening for this allele could be beneficial for preventing allopurinol induced SCARs. However, the implementation of HLA-B*58:01 screening requires caution in some populations, such as Japanese and European populations, because not all allopurinol induced SCARs patients carry the HLA-B*58:01 allele in those populations.

Study funding/potential competing interests

This work was supported by grants from the Academia Sinica Genomic Medicine Multicenter Study (40-05-GMM), Taiwan Biobank, Academia Sinica, and the National Health Research Institutes (NHIRD-102-066). All three funders are from Taiwan. We declare no other interests.

Historical incidence of allopurinol induced SCARs in 2001-04, compared with incidence among study participants

	Year			
Variable	2001	2002	2003	2004
Incidence (%) of allopurinol induced SCARs (95% CI)	0.32% (0.29% to 0.35%)	0.30% (0.27% to 0.33%)	0.28% (0.25% to 0.32%)	0.29% (0.26% to 0.32%)
P value comparing historical incidence and actual incidence among study participants*	0.0018	0.0026	0.0038	0.0040

*P values calculated by the two side, one sample binomial test.

Prevalence and compensation of academic leaders, professors, and trustees on publicly traded US healthcare company boards of directors: cross sectional study

Timothy S Anderson,[1] Chester B Good,[2] Walid F Gellad[3]

EDITORIAL by Rothman

[1]Department of Internal Medicine, University of Pittsburgh Medical Center, Pittsburgh, PA, USA
[2]Center for Health Equity Research and Promotion, VA Pittsburgh Healthcare System; VA Center for Medication Safety, Department of Veterans Affairs; University of Pittsburgh School of Medicine, Pittsburgh, PA, USA
[3]University of Pittsburgh Center for Pharmaceutical Policy and Prescribing and Division of General Internal Medicine; Center for Health Equity Research and Promotion, VA Pittsburgh Healthcare System, Pittsburgh, PA, USA
Correspondence to: W F Gellad, VA Pittsburgh Healthcare System, Pittsburgh, PA 15240, USA
wfg3@pitt.edu

Cite this as: *BMJ* 2015;351:h4826
doi: 10.1136/bmj.h4826

This is a summary of a paper that was published on thebmj.com as *BMJ* 2015;351:h4826

STUDY QUESTION

What is the prevalence and compensation of academic leaders, professors, and trustees on the boards of directors of publicly traded US healthcare companies?

SUMMARY ANSWER

Nearly 1 in 10 US for profit healthcare company directorships are held by academically affiliated individuals, including leaders, professors, and trustees from 85 major non-profit academic institutions. 41% of publicly traded US healthcare companies included at least one academically affiliated director, and these 279 directors received annual cash fees totaling over $54m (£35m; €48m) for serving as directors and owned over 59 million shares of company stock.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Academic leaders frequently serve on pharmaceutical industry boards of directors, resulting in conflicts of interest between their academic and industry roles. By looking beyond pharmaceuticals to examine the entire publicly traded US healthcare industry, this study is the first to highlight the complex challenge posed by a diverse set of academic leaders, professors, and trustees who face individual and institutional conflicts of interest as a result of their dual obligations to for profit companies and non-profit academic institutions.

Participants and setting

Directors of US pharmaceutical, biotechnology, medical equipment and supply, and healthcare provider companies publicly traded on the NASDAQ or New York Stock Exchange in 2013.

Design: Cross sectional study.

Primary outcomes

Prevalence, annual compensation, and beneficial stock ownership of directors with academic medical and research institution affiliations.

Main results and the role of chance

Out of 446 publicly traded US healthcare companies, 442 had available disclosure data, of which 180 (41%) had one or more academically affiliated directors. Overall, these 279 directors included 73 leaders, 121 professors, and 85 trustees affiliated with 85 geographically diverse non-profit academic institutions. Leaders included 17 chief executive officers, 15 university presidents, provosts, and chancellors, and eight medical school deans or presidents. Total annual compensation to academically affiliated directors for their services to companies was $54 995 786 (median individual compensation $193 000) and directors beneficially owned 59 831 477 shares of company stock (median 50 699 shares).

Bias, confounding, and other reasons for caution

Study methods were intentionally conservative, looking only at active relationships and excluding non-US faculty, emeritus faculty, academic advisory board members, and individuals with recent academic relationships. As our data were drawn from disclosures to the US Securities and Exchange Commission, they exclude privately held US companies and non-US healthcare companies, all of which may have academically affiliated board members. As a result of these two limitations, our study likely underreports the full scope of ties between industry directors and academia.

Generalisability to other populations

These results are specific to US healthcare companies and academia; further study is needed to determine if similar relationships exist in other regions.

Study funding/potential competing interests

WG was supported by a VA Health Services research and development career development award (CDA 09-207). This work represents the opinions of the authors alone and does not necessarily represent the views of the Department of Veterans Affairs or the US Government.

Compensation and beneficial stock ownership to academic leaders, professors, and trustees for serving as directors of publicly traded US healthcare companies

Academically affiliated directors	No of individuals	Total No of company directorships held	Median (interquartile range) annual compensation per directorship ($)*	Total No of beneficially owned stock shares*
Leaders, professors, and trustees	279	309	193 000 (102 000-271 000)	59 831 477
Leaders:	73	85	209 000 (103 000-271 000)	5 493 946
Hospital and health system chief executive officers	17	21	221 000 (152 000-277 000)	891 351
University and research institute presidents, provosts, and chancellors	15	17	185 000 (104 000-199 000)	1 801 756
Health science school deans and presidents	11	17	268 000 (105 000-305 000)	545 917
Professors	121	131	160 000 (82 000-259 000)	22 513 088
Academic trustees	85	93	227 000 (145 000-278 000)	31 824 443

$1.00 (£0.65; €0.89).
*Compensation excluded the two leaders, eight professors, and 15 academic trustees who held positions as company executive officers, as well as seven individuals appointed midway through the year. Compensation is rounded to the nearest $1000.