Korean Society for Health Promotion and Disease Prevention

2021년 대한임상건강증진학회 춘계학술대회

2021. 5. 30 (일)

칼슘제 복용은 심혈관 질환의 위험성을 높힌다? (Hot research talk)

명 승 권 (국립암센터)

골다공증 예방과 치료를 위한 칼슘섭취 가이드라인

- **National Osteoporosis Foundation (NOF) in US, Last Reviewed 02/26/2018, Accessed 05/10/2021**

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How Much Calcium Do You Need?

The amount of calcium you need every day depends on your age and sex.

WOMEN	
Age 50 & younger	1,000 mg* daily
Age 51 & older	1,200 mg* daily
MEN	
Age 70 & younger	1,000 mg* daily
Age 71 & older	1,200 mg* daily

**This includes the total amount of calcium you get from food and supplements.*

골다공증 예방과 치료를 위한 칼슘섭취 가이드라인

- **National Osteoporosis Foundation (NOF) in US, Last Reviewed 02/26/2018, Accessed 05/10/2021**

Calcium Supplements

The amount of calcium you need from a supplement depends on how much you get from food. Try to get the daily amount recommended from food and only supplement as needed to make up any shortfall. In general, you shouldn't take supplements that you don't need. If you get enough calcium from foods, don't take a supplement. There is no added benefit to taking more calcium than you need. Doing so may even carry some risks.

Calcium supplements are available without a prescription in a wide range of preparations (including chewable and liquid) and in different amounts. The best supplement is the one that meets your needs for convenience, cost, and availability. When choosing a supplement, keep the following in mind:

- **Choose brand-name supplements with proven reliability.** Look for labels that state "purified" or have the USP (United States Pharmacopeia) symbol. The "USP Verified Mark" on the supplement label means that the USP has tested and found the calcium supplement to meet its standards for purity and quality.
- **Read the product label carefully to determine the amount of *elemental calcium*,** which is the actual amount of calcium in the supplement, as well as how many doses or pills you have to take. When reading the label, pay close attention to the "amount per serving" and "serving size."
- **Calcium is absorbed best when taken in amounts of 500 – 600 mg or less.** This is the case for both foods and supplements. Try to get your calcium-rich foods and/or supplements in small amounts throughout the day, preferably with a meal. While it's not recommended, taking your calcium all at once is better than not taking it at all.
- **Take (most) calcium supplements with food.** Eating food produces stomach acid that helps your body absorb most calcium supplements. The one exception to the rule is calcium citrate, which can absorb well when taken with or without food.
- **When starting a new calcium supplement, start with a smaller amount to better tolerate it.** When switching supplements, try starting with 200-300 mg every day for a week, and drink an extra 6-8 ounces of water with it. Then gradually add more calcium each week.
- **Side effects from calcium supplements, such as gas or constipation may occur.** If increasing fluids in your diet does not solve the problem, try another type or brand of calcium. It may require trial and error to find the right supplement for you, but fortunately there are many choices.
- **Talk with your healthcare provider or pharmacist about possible interactions between prescription or over-the-counter medications and calcium supplements.**

골다공증 예방과 치료를 위한 칼슘섭취 가이드라인

- **American Association of Clinical Endocrinologists and American College of Endocrinology, 2020 Endocr Pract.**

R14. Counsel patients to maintain adequate dietary intake of calcium, to a total intake (including diet plus supplement, if needed) of 1,200 mg/day for women age ≥ 50 years **(Grade B; BEL 1, downgraded due to limited evidence).**

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National Health Service in UK

NHS

Sources of calcium include:

- milk, cheese and other dairy foods
- green leafy vegetables – such as curly kale, okra and spinach
- soya drinks with added calcium
- bread and anything made with fortified flour
- fish where you eat the bones – such as sardines and pilchards

How much calcium do I need?

Adults aged 19 to 64 need 700mg of calcium a day.

You should be able to get all the calcium you need from your daily diet.

What happens if I take too much calcium?

Taking high doses of calcium (more than 1,500mg a day) could lead to stomach pain and diarrhoea.

What does the Department of Health and Social Care advise?

You should be able to get all the calcium you need by eating a varied and balanced diet.

If you take calcium supplements, do not take too much as this could be harmful.

Taking 1,500mg or less a day is unlikely to cause any harm.

Page last reviewed: 02 August 2020
Next review due: 02 August 2023

골다공증 예방과 치료를 위한 칼슘섭취 가이드라인

대한골대사학회 골다공증 진료지침 2018

3. 칼슘의 영양섭취기준

칼슘은 섭취가 가장 적은 영양소 중 하나로 국민건강영양조사에서 칼슘 섭취량은 권장섭취량의 70.4%였고, 50세 이상 남녀의 식이 칼슘섭취량은 470 mg였다. 2015년 보건복지부와 한국영양학회의 칼슘 권장섭취량은 다음과 같다(표 11-2). 미국 NOF에서는 50~70세 남성에서 1일 1,000 mg, 51세 이상 여성과 71세 이상 남성에서 1일 1,200 mg의 칼슘 섭취를 권장하고 있다. 음식을 통한 칼슘 섭취가 부족한 경우 칼슘보충제의 투여로 부족한 부분만 보충하면 된다. 대한골대사학회에서는 1일 800~1,000 mg의 칼슘 섭취를 권장한다.

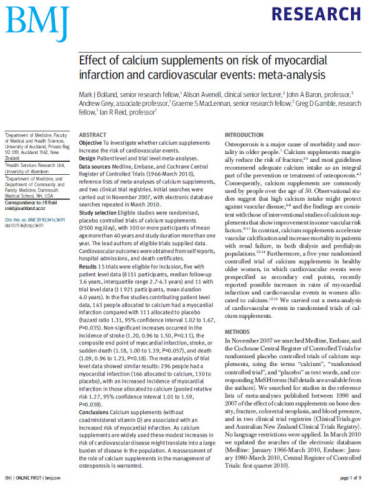
4. 이상 반응

칼슘보충제 투여 시 일반적으로 위장장애나 변비 외에 심한 이상 반응은 없으나 신결석, 고칼슘뇨증 환자에서는 칼슘 투여를 줄이거나 중단해야 한다. 칼슘보충제 1,000 mg과 비타민D 400 IU를 투여하면 신결석의 위험이 투여 받지 않은 군에 비해 17% 증가한다는 보고가 있다. 한편 성인이 식사를 통해 칼슘 섭취를 많이 하면 신결석 위험은 감소한다.

칼슘보충제 투여와 심혈관질환과의 연관성에 대해 많은 논란이 있다. 칼슘 섭취가 많으면 심혈관질환의 위험이 감소한다는 연구가 있는 반면에 심혈관질환의 위험이 증가한다는 연구도 있다. 또한 칼슘 섭취가 부족하면 전체 사망률과 심혈관질환의 사망률이 증가한다는 연구도 있다. 최근 무작위시험과 전향적 코호트들을 분석한 연구에서 건강한 성인이 하루 2,000~2,500 mg의 칼슘을 섭취하는 것은 심혈관질환의 위험과 연관이 없다고 보고하였으며, 최근 영국의 전향적 코호트연구에서도 칼슘/비타민D 보충제 섭취와 심혈관질환에 의한 사망이나 병원 입원의 위험도는 증가하지 않는다고 보고하였다.

우리나라 국민건강영양조사에서 성인의 식이 칼슘 섭취가 하루 300 mg 이하이거나 1,200 mg 이상인 경우 심혈관질환 위험도 수치가 증가할 수 있다는 연구가 있으며, 한국인 코호트를 평균 9년간 추적한 결과 50세 이상 여성에서 식이 칼슘 섭취가 증가하면 심혈관질환의 위험도가 낮아진다는 연구도 있다.

칼슘보충제는 심근경색증 위험 높임
- 2010, Bolland et al

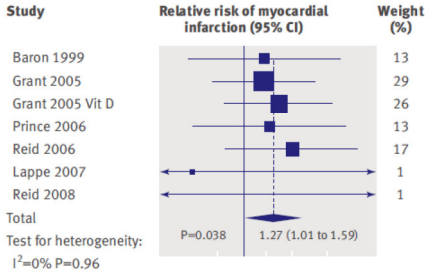


BMJ **RESEARCH**

Effect of calcium supplements on risk of myocardial infarction and cardiovascular events: meta-analysis

Mark J Bolland, senior research fellow,[1] Alison Avenell, clinical senior lecturer,[2] John A Baron, professor,[3] Andrew Grey, associate professor,[1] Graeme S MacLennan, senior research fellow,[2] Greg D Gamble, research fellow,[1] Ian R Reid, professor[1]

- **Meta-analysis of 7 RCTs**
  - Increased risk of MI by 27%



Bolland et al, British Medical Journal, 2010.

칼슘보충제는 심근경색증이나 관상동맥심장질환과 관련없음
- 2015, Lewis et al

ORIGINAL ARTICLE JBMR®

The Effects of Calcium Supplementation on Verified Coronary Heart Disease Hospitalization and Death in Postmenopausal Women: A Collaborative Meta-Analysis of Randomized Controlled Trials

Joshua R Lewis,[1,2] Simone Radavelli-Bagatini,[1,2] Lars Rejnmark,[3] Jian Sheng Chen,[4] Judy M Simpson,[5] Joan M Lappe,[6] Leif Mosekilde,[7] Ross L Prentice,[7] and Richard L Prince[1,2]

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ABSTRACT

Calcium supplementation, particularly with vitamin D, has been an approved public health intervention to reduce fracture risk. Enthusiasm for this intervention has been mitigated by meta-analyses suggesting that calcium supplementation with or without vitamin D increases myocardial infarction (MI) risk; however, concern has been raised over the design of these meta-analyses. We, therefore, undertook a meta-analysis of randomized controlled trials with placebo or no-treatment control groups to determine if these supplements increase all-cause mortality and coronary heart disease (CHD) risk including MI, angina pectoris and acute coronary syndrome, and chronic CHD verified by clinical review, hospital record, or death certificate in elderly women. The Cochrane Central Register of Controlled Trials, MEDLINE, and EMBASE databases were searched from January 1, 1966, to May 24, 2013, for potentially eligible studies, reference lists were checked, and trial investigators were contacted where additional unpublished data were required. The search yielded 661 potentially eligible reports of which 18 met the inclusion criteria and contributed information on 63,563 participants with 3390 CHD events and 4157 deaths. Two authors extracted the data independently with trial data combined using random-effects meta-analysis to calculate the relative risk (RR). Five trials contributed CHD events with pooled relative RR of 1.02 (95% confidence interval (CI), 0.96–1.09; $p = 0.51$). Seventeen trials contributed all-cause mortality data with pooled RR of 0.96 (95% CI, 0.91–1.02; $p = 0.18$). Heterogeneity among the trials was low for both primary outcomes ($I^2 = 0\%$). For secondary outcomes, the RR for MI was 1.08 (95% CI, 0.92–1.26; $p = 0.32$), angina pectoris and acute coronary syndrome 1.09 (95% CI, 0.95–1.24; $p = 0.22$) and chronic CHD 0.92 (95% CI, 0.73–1.15; $p = 0.46$). In conclusion, current evidence does not support the hypothesis that calcium supplementation with or without vitamin D increases coronary heart disease or all-cause mortality risk in elderly women. © 2014 American Society for Bone and Mineral Research.

KEY WORDS: CALCIUM SUPPLEMENTATION; VERIFIED CORONARY HEART DISEASE; POSTMENOPAUSAL WOMEN; ALL-CAUSE MORTALITY

Introduction

A recent Institute of Medicine review of the scientific literature concluded that available scientific evidence supports a key role of calcium and vitamin D in the maintenance of skeletal health and recommended a daily intake of 1.2 g of calcium and 800 IU of vitamin D in elderly women.[1] To meet these requirements, calcium supplements with or without vitamin D are being widely used by elderly women.[2] However, a meta-analysis of randomized controlled trials (RCTs) has reported that calcium supplementation alone increases the risk of myocardial infarction by 27%.[3] These authors then updated the previous report by including a number of RCTs of calcium supplements with vitamin D and concluded that these supplements increased the risk of myocardial infarction by 21%.[4] Concerns regarding the approach taken in these meta-analyses have been raised.[5]

Myocardial infarction is only one of several clinical presentations of coronary artery disease that is best captured using the

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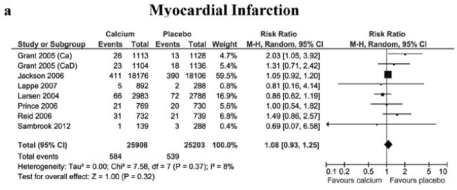
Additional Supporting Information may be found in the online version of this article.
Journal of Bone and Mineral Research, Vol. 30, No. 1, January 2015, pp 165–175
DOI: 10.1002/jbmr.2311

- **Meta-analysis of 7 RCTs**
  - No significant association between calcium supplements and myocardial infarction

- **Meta-analysis of 5 RCTs**
  - No significant association between calcium supplements and coronary heart disease



Lewis et al, JBMR, 2015.

논쟁

- **Lewis et al's criticism against Bolland et al's meta-analysis**
  - None of the trials included in Bolland et al's meta-analysis had cardiovascular disease (CVD) as its primary endpoint.
  - Over 65% of all the heart attacks were self-reported.

- **Bolland et al's response to Lewis et al's criticism**
  - They adjusted for potential confounders in secondary analyses, the results did not change, and considerable amounts of data on heart attacks were obtained from death certificates and medical records.

Nordin and Lewis et al, Osteoporosis Int, 2011

논쟁

- **Bolland et al's criticism against Lewis et al's meta-analysis**

  - The results of Lewis et al's meta-analysis are similar to those from their previous meta-analysis, when an open-label study is excluded.

Bolland et al, J Bone Miner Res, 2015

칼슘보충제는 심혈관질환과 관련없음
- 2016, Chung et al

REVIEW — Annals of Internal Medicine

Calcium Intake and Cardiovascular Disease Risk
An Updated Systematic Review and Meta-analysis

Mei Chung, MPH, PhD; Alice M. Tang, SCM, PhD; Zhuoxun Fu, MPH; Ding Ding Wang, MPH; and Sydne Jennifer Newberry, MS, PhD

Background: Conflicting evidence exists regarding potential cardiovascular risks associated with high levels of calcium intake.

Purpose: To update and reanalyze 2 systematic reviews to examine the effects of calcium intake on cardiovascular disease (CVD) among generally healthy adults.

Data Sources: MEDLINE; Cochrane Central Register of Controlled Trials; Scopus, including EMBASE; and previous evidence reports from English-language publications from 1966 to July 2016.

Study Selection: Randomized trials and prospective cohort and nested case–control studies with data on dietary or supplemental intake of calcium, with or without vitamin D, and cardiovascular outcomes.

Data Extraction: Study characteristics and results extracted by 1 reviewer were confirmed by a second reviewer. Two raters independently assessed risk of bias.

Data Synthesis: Overall risk of bias was low for the 4 randomized trials (n 10 publications) and moderate for the 27 observational studies included. The trials did not find statistically significant differences in risk for CVD events or mortality between groups receiving supplements of calcium or calcium plus vitamin D and those receiving placebo. Cohort studies showed no consistent dose–response relationships between total, dietary, or supplemental calcium intake levels and cardiovascular mortality and highly inconsistent dose–response relationships between calcium intake and risks for total stroke or stroke mortality.

Limitations: CVD disease outcomes were secondary end points in all trials. Dose–response meta-regression analysis of cohort studies was limited by potential confounding, ecological bias, and imprecise measures of calcium exposures. Data were scarce regarding very high calcium intake–that is, beyond recommended tolerable upper intake levels.

Conclusion: Calcium intake within tolerable upper intake levels (2000 to 2500 mg/d) is not associated with CVD risk in generally healthy adults.

Primary Funding Source: National Osteoporosis Foundation.

Ann Intern Med. 2016;165:856-866. doi:10.7326/M16-1165. www.annals.org
For author affiliations, see end of text.
This article was published at www.annals.org on 25 October 2016.

Calcium is a nutrient essential for maintaining bone health. A small proportion of total body calcium (less than 1%) also regulates vascular contraction and vasodilation, muscle function, nerve transmission, intracellular signaling, and hormonal secretion. Vitamin D promotes calcium absorption in the gut and maintains adequate serum calcium and phosphate concentrations, enabling normal bone mineralization and preventing hypocalcemic tetany (1).

Although adequate calcium and vitamin D intake is critical for maintaining bone health, the role of calcium and vitamin D supplementation in older adults is unclear. Some systematic reviews showed that combined calcium and vitamin D supplementation reduced the risk for fractures in older adults (2, 3), whereas more recent systematic reviews reported inconsistent effects for fractures across randomized, controlled trials (4, 5). Experts have raised concerns about a potential effect of a high intake of calcium (with or without vitamin D) from foods and supplements on cardiovascular disease (CVD) outcomes (6–8). A meta-analysis of both study- and patient-level data from randomized trials showed that calcium with or without vitamin D supplementation increased the risk for myocardial infarction (pooled relative risk, 1.24 [95% CI, 1.07 to 1.45]) and stroke (pooled relative risk, 1.15 [CI, 1.00 to 1.32]) (9, 10). However, a more recent meta-analysis showed that calcium with or without vitamin D supplementation had no statistically significant effects on coronary heart disease events (pooled relative risk, 1.02 [CI, 0.96 to 1.09]) or mortality (pooled relative risk, 1.04 [CI, 0.88 to 1.21]) (11). Many researchers have questioned the strength of the body of evidence linking supplemental calcium intake with CVD risk, noting that cardiovascular outcomes have not been the primary end point of any trial investigating calcium or calcium and vitamin D supplementation to date (12, 13).

To inform a joint position statement from the National Osteoporosis Foundation (NOF) and American Society for Preventive Cardiology, NOF commissioned a focused update and reanalysis of 2 broader evidence reports examining the effects of calcium and vitamin D on a wide range of clinical and intermediate outcomes (5, 14). This update addresses the effects of calcium intake (from dietary or supplemental sources), alone or in combination with vitamin D, on CVD risk in generally healthy adults.

METHODS

This systematic review implemented the same methodology as the 2009 evidence report examining

See also:
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Editorial comment 884
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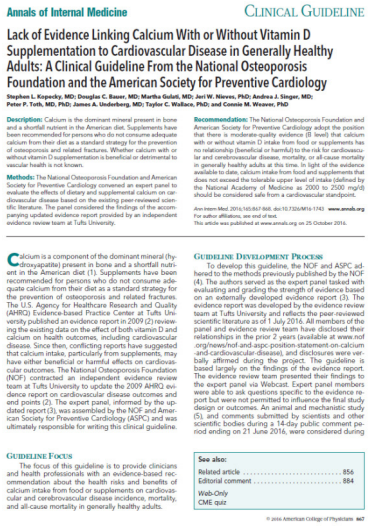
- **No significant differences** in risk for CVD events between groups receiving calcium or calcium plus vitamin D and those receiving placebo in the meta-analysis of 4 randomized trials, as well as in the meta-analysis of 26 cohort studies and 1 nested case-control study.
- Funded by the National Osteoporosis Foundation (NOF).

Chung et al, Ann Int Med, 2016.

칼슘보충제는 심혈관질환과 관련없음
- NOF and ASPC based on the findings from 2016, Chung et al



Annals of Internal Medicine — CLINICAL GUIDELINE

Lack of Evidence Linking Calcium With or Without Vitamin D Supplementation to Cardiovascular Disease in Generally Healthy Adults: A Clinical Guideline From the National Osteoporosis Foundation and the American Society for Preventive Cardiology

Stephen L. Kopecky, MD; Douglas C. Bauer, MD; Martha Gulati, MD; Jori W. Nieves, PhD; Andrea J. Singer, MD; Peter P. Toth, MD, PhD; James A. Underberg, MD; Taylor C. Wallace, PhD; and Connie M. Weaver, PhD

Description: Calcium is the dominant mineral present in bone and a shortfall nutrient in the American diet. Supplements have been recommended for persons who do not consume adequate calcium from their diet as a standard strategy for the prevention of osteoporosis and related fractures. Whether calcium with or without vitamin D supplementation is beneficial or detrimental to vascular health is not known.

Methods: The National Osteoporosis Foundation and American Society for Preventive Cardiology convened an expert panel to evaluate the effects of dietary and supplemental calcium on cardiovascular disease based on the existing peer-reviewed scientific literature. The panel considered the findings of the accompanying updated evidence report provided by an independent evidence review team at Tufts University.

Recommendation: The National Osteoporosis Foundation and American Society for Preventive Cardiology adopt the position that there is moderate-quality evidence (B level) that calcium with or without vitamin D intake from food or supplements has no relationship (beneficial or harmful) to the risk for cardiovascular and cerebrovascular disease, mortality, or all-cause mortality in generally healthy adults at this time. In light of the evidence available to date, calcium intake from food and supplements that does not exceed the tolerable upper level of intake (defined by the National Academy of Medicine as 2000 to 2500 mg/d) should be considered safe from a cardiovascular standpoint.

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For author affiliations, see end of text.

This article was published at www.annals.org on 25 October 2016.

Calcium is a component of the dominant mineral (hydroxyapatite) present in bone and a shortfall nutrient in the American diet (1). Supplements have been recommended for persons who do not consume adequate calcium from their diet as a standard strategy for the prevention of osteoporosis and related fractures. The U.S. Agency for Healthcare Research and Quality (AHRQ) Evidence-based Practice Center at Tufts University published an evidence report in 2009 (2) reviewing the existing data on the effect of both vitamin D and calcium on health outcomes, including cardiovascular disease. Since then, conflicting reports have suggested that calcium intake, particularly from supplements, may have either beneficial or harmful effects on cardiovascular outcomes. The National Osteoporosis Foundation (NOF) contracted an independent evidence review team at Tufts University to update the 2009 AHRQ evidence report on cardiovascular disease outcomes and end points (2). The expert panel, informed by the updated report (3), was assembled by the NOF and American Society for Preventive Cardiology (ASPC) and was ultimately responsible for writing this clinical guideline.

GUIDELINE DEVELOPMENT PROCESS

To develop this guideline, the NOF and ASPC adhered to the methods previously published by the NOF (4). The authors served as the expert panel tasked with evaluating and grading the strength of evidence based on an externally developed evidence report (3). The evidence report was developed by the evidence review team at Tufts University and reflects the peer-reviewed scientific literature as of 1 July 2016. All members of the panel and evidence review team have disclosed their relationships in the prior 2 years (available at www.nof.org/news/nof-and-aspc-position-statement-on-calcium-and-cardiovascular-disease), and disclosures were verbally affirmed during the project. The guideline is based largely on the findings of the evidence report. The evidence review team presented their findings to the expert panel via Webcast. Expert panel members were able to ask questions specific to the evidence report but were not permitted to influence the final study design or outcomes. An animal and mechanistic study (5), and comments submitted by scientists and other scientific bodies during a 14-day public comment period ending on 21 June 2016, were considered during

GUIDELINE FOCUS

The focus of this guideline is to provide clinicians and health professionals with an evidence-based recommendation about the health risks and benefits of calcium intake from food or supplements on cardiovascular and cerebrovascular disease incidence, mortality, and all-cause mortality in generally healthy adults.

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- Based on the existing peer-reviewed scientific literature including Chung et al's evidence report, **the NOF and the American Society for Preventive Cardiology (ASPC)** announced a clinical guideline that there is moderate-quality evidence that calcium with or without vitamin D intake from food or supplements has **no association** with CVD in generally healthy adults.

Kopecky et al, Ann Int Med, 2016.

골다공증 예방·치료 칼슘제, 심혈관질환 발생 위험성 높여

입력 : 2021-03-23 03:00:00 | 수정 : 2021-03-22 10:31:03

▲ 명승권(왼쪽), 김홍배 교수

골다공증 예방 및 치료에 많이 사용되는 칼슘제 복용시 협심증 및 심근경색증 등 심혈관질환 발생 위험이 높아진다는 연구결과가 나왔다.

국립암센터 국제암대학원대학교 대학원장 명승권 가정의학과 교수와 한양대학교 명지병원 가정

nutrients

MDPI

Review

Calcium Supplements and Risk of Cardiovascular Disease: A Meta-Analysis of Clinical Trials

Seung-Kwon Myung [1,2,3,*†], Hong-Bae Kim [4,†], Yong-Jae Lee [5], Yoon-Jung Choi [6] and Seung-Won Oh [7]

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Abstract: Background: Recent systematic reviews and meta-analyses of randomized, double-blind, placebo-controlled trials (double-blind, placebo-controlled RCTs) have reported controversial findings regarding the associations between calcium supplements on the risk of cardiovascular disease (CVD). This meta-analysis aimed to investigate the association between them. Methods: We searched PubMed, EMBASE, the Cochrane Library, and the bibliographies of relevant articles for double-blind, placebo-controlled RCTs in November, 2020. Relative risks (RRs) with 95% confidence intervals (CIs) for the risk of cardiovascular disease were calculated using a random effects model. The main outcomes were CVD, coronary heart disease (CHD), and cerebrovascular disease. Results: A total of 13 double-blind, placebo-controlled RCTs (n = 28,935 participants in an intervention group and 14,243 in a control group)) were included in the final analysis. Calcium supplements significantly increased the risk of CVD (RR 1.15, 95% CI 1.06–1.25, I2 = 0.0%, n = 14) and CHD (RR 1.16, 95% CI 1.05–1.28, I2 = 0.0%, n = 9) in double-blind, placebo-controlled RCTs, specifically in healthy postmenopausal women. In the subgroup meta-analysis, dietary calcium intake of 700–1000 mg per day or supplementary calcium intake of 1000 mg per day significantly increased the risk of CVD and CHD. Conclusions: The current meta-analysis found that calcium supplements increased a risk of CVD by about 15% in healthy postmenopausal women.

Keywords: calcium supplements; cardiovascular disease; randomized controlled trials; meta-analysis

check for updates

Citation: Myung, S.-K.; Kim, H.-B.; Lee, Y.-J.; Choi, Y.-J.; Oh, S.-W. Calcium Supplements and Risk of Cardiovascular Disease: A Meta-Analysis of Clinical Trials. *Nutrients* **2021**, *13*, 368. https://doi.org/10.3390/nu13020368

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1. Introduction

Current guidelines for the prevention and treatment of osteoporosis recommend adequate intakes of dietary calcium ranging 700–1200 mg/day for adults aged 50 and older from health and academic organizations such as the National Osteoporosis Foundation in 2014, American Association of Clinical Endocrinologists and American College of Endocrinology in 2016, and National Osteoporosis Guideline Group in 2017 [1–3]. If dietary intakes are insufficient, calcium supplements are recommended. However, Bolland et al. raised concerns that calcium supplements were associated with an increased risk of myocardial infarction by about 30% in their meta-analysis of randomized, double-blind,

- 2021년 1월, 명승권 등
- Nutrients (SCIE IF = 4.5)

골다공증 예방 및 치료에 사용되는 칼슘제, 심혈관질환 발생 위험성 높여

- 국립암센터 명승권 교수 연구팀, 메타분석 공동 연구 -

골다공증 예방 및 치료에 많이 사용되고 있는 칼슘제를 복용하는 경우 협심증 및 심근경색증 등의 심혈관질환 발생 위험을 높인다는 연구결과가 나왔다.

국립암센터 국제암대학원대학교(총장 서홍관) 대학원장 명승권 교수(의학박사, 가정의학과 전문의)와 한양대학교 명지병원 가정의학과 김홍배 교수(공동 제1저자)가 공동으로 1990년부터 2013년까지 국제학술지에 발표된 13편의 임상시험을 메타분석한 결과 이같이 확인됐다고 밝혔다.

연구팀은 주요 의학데이터베이스인 펍메드(PubMed), 엠베이스(EMBASE) 및 코크란 라이브러리(Cochrane Library)에서 문헌검색을 통해 최종적으로 선정된 13편의 무작위 이중맹검 위약대조 임상시험(Randomized, double-blind, placebo-controllled trial)의 연구결과를 종합해 메타분석했다. 분석결과, 칼슘제를 복용한 경우 가짜약인 위약(placebo)을 복용한 경우보다 심혈관질환(관상동맥질환과 뇌혈관질환을 포함)의 위험성이 15%(상대위험도 1.15, 95% 신뢰구간 1.06-1.25) 높은 것으로 나타났다.

심혈관질환을 관상동맥질환과 뇌혈관질환으로 구분해 메타분석한 결과 관상동맥질환의 위험성만 통계적으로 유의하게 높았다.(상대위험도 1.16, 95% 신뢰구간 1.05-1.28) 또한, 기저질환이 있는 대상자의 경우 칼슘제의 복용과 심혈관질환의 위험성 사이에 통계적인 유의성을 보이지는 않았으나, 폐경 후 건강한 여성에서는 심혈관질환의 위험성이 통계적으로 의미

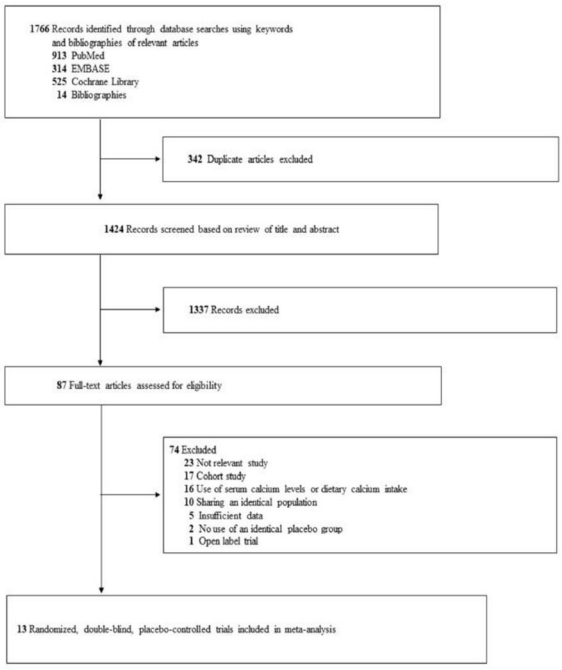

Figure 1. Study selection.

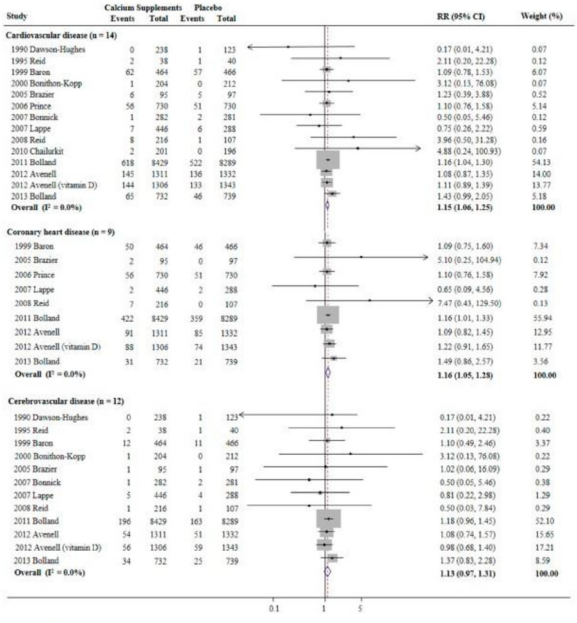

Figure 2. Use of calcium supplements and risk of cardiovascular disease in a random-effects meta-analysis of randomized controlled trials. RR, relative risk; CI, confidence interval. Avenell et al.'s trial [25] used both calcium alone and calcium plus vitamin D in the supplementation groups. Thus, a total of 14 trials were included in the analysis.

Table 2. Differences in the main findings and study characteristics among previous systematic reviews and meta-analyses and the current systematic review and meta-analysis of clinical trials on calcium supplementation and the risk of cardiovascular disease.

	2010, Bolland et al. [4]	2011, Bolland et al. [5]	2013, Mao et al. [28]	2015, Lewis et al. [6]	2016, Chung et al. [10]	Current Meta-Analysis
Conclusion on Calcium Supplementation and Risk of CVD	**Increase**	**Increase**	**Might Increase**	**Not Increase**	**Not Associated, Small Risk and Not Clinically Important, if Any**	**Increase**
Main Findings: RR (95% CI), Number of Included Trials (Reference No.) *, Interpretation in Each Article						
Myocardial Infarction (MI)	- 1.27 (1.01–1.59) - 7 (16, 19, 21, 22, 25, 26) - Increased risk	- 1.24 (1.07–1.45) - 8 (16, 19, 21, 22, 24, 25, 26) - Increased risk	- 1.28 (0.97–1.68) - 8 (16, 19, 21, 22, 24, 25, 26) - Non-significantly increased risk	- 1.08 (0.93–1.25) - 8 (19, 21, 24, 25, 26, 2004 Larsen, 2012 Sambrook) - No increased risk	n.a.	- 1.25 (1.07–1.45) - 9 (16, 18, 19, 21, 22, 24, 25, 26) - Significantly increased risk
Stroke	- 1.12 (0.92–1.36) - 8 (1993 Reid, 16, 19, 20, 21, 25, 26) - No increased risk	- 1.15 (1.00–1.32) - 9 (1993 Reid, 16, 19, 20, 21, 24, 25, 26) - Increased risk	- 1.14 (0.90–1.46) - Not specified - Non-significantly increased risk	n.a.	n.a.	- 1.13 (0.97–1.31) - 12 (14–18,20–22,24–26) - Non-significantly increased risk
Cardiovascular disease (CVD): coronary heart disease (CHD) plus stroke	- 1.12 (0.97–1.30) - 8 (1993 Reid, 16, 19, 21, 22, 25, 26) - No increased risk (composite end point of MI, stroke, and sudden death)	- 1.15 (1.03–1.27) - 10 (1993 Reid, 16, 19, 20, 21, 22, 24, 25, 26) - Increased risk (MI or stroke)	- 1.16 (0.97–1.40) - Not specified - Non-significantly increased risk (major CV events)	- 1.02 (0.96–1.09) - 6 (19, 24, 25, 2004 Larsen, 2012 Sambrook) - No increased risk (CHD)	- No meta-analysis performed - 4 (2011 Lewis, 24, 25, 26) - No statistically significant difference	- 1.15 (1.06–1.25) - 14 (14–26) - Significantly increased risk (CHD plus stroke)

Table 2. *Cont.*

	2010, Bolland et al. [4]	2011, Bolland et al. [5]	2013, Mao et al. [28]	2015, Lewis et al. [6]	2016, Chung et al. [10]	Current Meta-Analysis
Conclusion on Calcium Supplementation and Risk of CVD	**Increase**	**Increase**	**Might Increase**	**Not Increase**	**Not Associated, Small Risk and Not Clinically Important, if Any**	**Increase**
Main Findings: RR (95% CI), Number of Included Trials (Reference No.) *, Interpretation in Each Article						
Funding Source	The Health Research Council of New Zealand and the University of Auckland School of Medicine Foundation	The Health Research Council of New Zealand and the University of Auckland School of Medicine Foundation	National "Eleven Five" "Significant new drugs creation" special science and technology major, a major national science and technology projects, etc.	Not described	National Osteoporosis Foundation through Pfizer Consumer Healthcare in U.S.	None

* Ref. [15]—1995 Reid et al. [16]—1999 Baron et al. [18]—2005 Brazier et al. [19]—2006 Prince et al. [20]—2007 Bonnick et al. [21]—2007 Lappe et al. [22]—2008 Reid et al. [24]—2011 Bolland et al. (WHI data) (=2006 Jackson et al.), [25]—2012 Avenell et al. [26]—2013 Bolland et al. (=2006 Reid et al.); Bolland et al.'s meta-analysis included Grant et al.'s trial, which is the first report of the RECORD trial. Ref. [25]—2012 Avenell et al. is the long-term follow-up report for the same trial. In Bolland et al.'s meta-analyses in 2010 and 2011, Grant et al.'s trial (=Ref. [25] 2012 Avenell et al.) was counted as two trials because it reported two findings from the RECORD trial calcium vs. placebo arms and calcium plus vitamin D vs. placebo plus vitamin D arms. 2004 Larsen et al. (open-label trial: a non-placebo control group used), 2012 Sambrook et al. (open-label trial a non-placebo control group used); n.a., not available.

있게 높아지는 것으로 나타났다.

한편, 현재 건강 및 의학 관련 학계에서는 골다공증의 예방과 치료를 목적으로 50세 이상의 성인에서 하루에 700-1200 mg (밀리그램)의 칼슘을 섭취할 것으로 권장하고 있다. 음식으로 섭취가 부족한 경우에도 보충제로서 칼슘제를 복용할 것을 권장하고 있다.

하지만, 2010년에 영국의학협회지(British Medical Journal)에 7편의 임상시험을 종합한 메타분석 결과 칼슘제를 복용하는 경우 심근경색증의 위험이 약 30% 정도 높아지는 것으로 보고됐다. 이와는 다르게 후속으로 발표된 메타분석 논문에서는 칼슘제 복용과 심혈관질환 위험은 관련성이 없다는 결과가 나와 논란이 되기도 했다.

연구를 주도한 책임저자 명승권 교수는 "이처럼 메타분석 논문들의 연구결과가 상이한 이유는 메타분석에 포함된 개별논문들의 선택기준, 연구대상자 특성 및 출판되지 않은 데이터의 포함 여부 등에 기인한다" 라고 말했다.

명승권 교수는 이어 "이번 결과는 음식이 아닌 칼슘제의 형태로 칼슘을 보충하는 경우, 혈청 칼슘농도가 장시간 동안 높아지는데, 이로 인해 혈관의 석회화 위험성이 높아져 심혈관질환을 초래할 수 있다는 생물학적 기전으로 해석하고 있다. 또 다른 기전으로 혈액 내 칼슘은 혈관윤고에 관여하기 때문에 과도한 칼슘의 섭취는 결국 심혈관질환의 위험성을 높일 수 있다." 라며 가능한 기전에 대해 설명했다.

명 교수는 아울러 "예전 연구의 결과에 따라 서양에서는 폐경 후 여성의 반 정도, 우리나라에서도 적지 않은 여성들이 골다공증이나 골절을 예방하거나 치료할 목적으로 칼슘제를 복용하고 있다." 라며 "하지만 최근에 발표된 임상시험의 메타분석 연구에 따르면, 칼슘제나 비타민D 제제의 복용이 골다공증 등으로 인한 골절의 빈도를 낮추지 못하는 것으로 나타나는 등, 최근 10여년 이상 발표된 연구결과는 예전과 다르게 나오기 시작했

다. 그래서, 2018년에 미국의 복지부 산하 질병예방서비스 특별위원회(USPSTF)에서는 방대한 최신 연구결과를 검토한 후, 칼슘이나 비타민D를 (음식이 아닌) 약제의 형태로 보충하는 것은 골절 예방에 효과가 없다고 결론을 내렸는데, 이번에 우리의 연구결과 역시 맥락이 같다. 반면에, 수십만명의 대규모의 사람을 대상으로 한 관찰연구 결과, 음식으로부터 칼슘을 섭취하는 것은 문제가 없기 때문에, 알약과 같은 보충제가 아니라 칼슘이 풍부한 음식 즉, 우유 및 유제품(요구르트, 치즈 등), 멸치와 같은 뼈째 먹는 생선, 배추/시금치/브로콜리 등의 질푸른 채소, 김/다시마/미역 등의 해조류, 콩류 등을 자주 충분히 섭취하면서, 햇볕을 10분 이상 쬐며 걷기나 달리기 등 유산소 운동을 규칙적으로 시행함으로써 골다공증이나 골절을 예방할 수 있다. 특히, 흡연과 저체중도 골다공증의 발생을 높이기 때문에 금연하고, 표준체중을 유지해야 한다. 다시 한번 강조하면, 칼슘이나 비타민D를 건강기능식품이나 약의 형태로 먹지 말아야 한다." 라며 연구의 임상적 의의를 강조했다.

공동 제1저자인 김홍배 교수는 "이번 연구는 현재까지 발표된 메타분석 논문들 가운데 가장 많은 임상시험을 포함한 포괄적인 메타분석이다" 라며, "심혈관질환 종류, 연구대상자 특성, 성별, 나이, 지역, 복용기간, 복용량, 연구의 질적 수준 등 다양한 요인별로 메타분석을 시행한 결과, 칼슘제의 복용은 심혈관질환의 위험성을 약 15% 높이는 것으로 나왔다." 라고 이번 메타분석 연구의 장점을 강조했다.

이번 연구결과는 SCIE 국제학술지인 영양소(Nutrients, IF 4.5)에 2021년 1월 발표했다.

*논문링크: https://doi.org/10.3390/nu13020368

칼슘보충제와 골절(2017, JAMA)

JAMA | Original Investigation

Association Between Calcium or Vitamin D Supplementation and Fracture Incidence in Community-Dwelling Older Adults
A Systematic Review and Meta-analysis

Jia-Guo Zhao, MD; Xian-Tie Zeng, MD; Jia Wang, MD; Lin Liu, MD

Supplemental content

IMPORTANCE The increased social and economic burdens for osteoporosis-related fractures worldwide make the prevention of such injuries a major public health goal. Previous studies have reached mixed conclusions regarding the association between calcium, vitamin D, or combined calcium and vitamin D supplements and fracture incidence in older adults.

OBJECTIVE To investigate whether calcium, vitamin D, or combined calcium and vitamin D supplements are associated with a lower fracture incidence in community-dwelling older adults.

DATA SOURCES The PubMed, Cochrane library, and EMBASE databases were systematically searched from the inception dates to December 24, 2016, using the keywords *calcium*, *vitamin D*, and *fracture* to identify systematic reviews or meta-analyses. The primary randomized clinical trials included in systematic reviews or meta-analyses were identified, and an additional search for recently published randomized trials was performed from July 16, 2012, to July 16, 2017.

STUDY SELECTION Randomized clinical trials comparing calcium, vitamin D, or combined calcium and vitamin D supplements with a placebo or no treatment for fracture incidence in community-dwelling adults older than 50 years.

DATA EXTRACTION AND SYNTHESIS Two independent reviewers performed the data extraction and assessed study quality. A meta-analysis was performed to calculate risk ratios (RRs), absolute risk differences (ARDs), and 95% CIs using random-effects models.

MAIN OUTCOMES AND MEASURES Hip fracture was defined as the primary outcome. Secondary outcomes were nonvertebral fracture, vertebral fracture, and total fracture.

RESULTS A total of 33 randomized trials involving 51 145 participants fulfilled the inclusion criteria. There was no significant association of calcium or vitamin D with risk of hip fracture compared with placebo or no treatment (calcium: RR, 1.53 [95% CI, 0.97 to 2.42], ARD, 0.01 [95% CI, 0.00 to 0.01]; vitamin D: RR, 1.31 [95% CI, 0.99 to 1.47], ARD, 0.00 [95% CI, −0.00 to 0.01]). There was no significant association of combined calcium and vitamin D with hip fracture compared with placebo or no treatment (RR, 1.09 [95% CI, 0.85 to 1.39], ARD, 0.00 [95% CI, −0.00 to 0.00]). No significant associations were found between calcium, vitamin D, or combined calcium and vitamin D supplements and the incidence of nonvertebral, vertebral, or total fractures. Subgroup analyses showed that these results were generally consistent regardless of the calcium or vitamin D dose, sex, fracture history, dietary calcium intake, and baseline serum 25-hydroxyvitamin D concentration.

CONCLUSIONS AND RELEVANCE In this meta-analysis of randomized clinical trials, the use of supplements that included calcium, vitamin D, or both compared with placebo or no treatment was not associated with a lower risk of fractures among community-dwelling older adults. These findings do not support the routine use of these supplements in community-dwelling older people.

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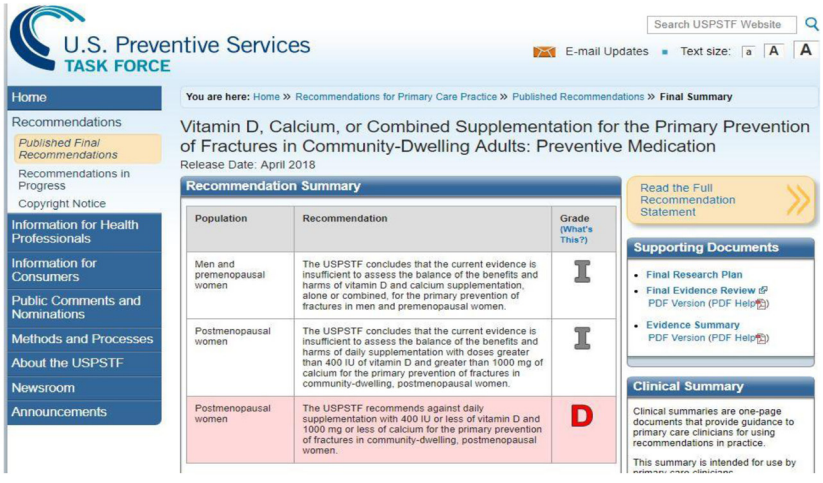
▪33편의 임상시험 메타분석

- 칼슘이나 비타민D 보충제는 단독으로 사용하던 복합으로 사용하던 골절 위험성을 낮추지 못해 권장할 수 없음.

미국 질병예방서비스특별위원회(2018년 4월)



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Vitamin D, Calcium, or Combined Supplementation for the Primary Prevention of Fractures in Community-Dwelling Adults: Preventive Medication

Release Date: April 2018

Recommendation Summary

Population	Recommendation	Grade (What's This?)
Men and premenopausal women	The USPSTF concludes that the current evidence is insufficient to assess the balance of the benefits and harms of vitamin D and calcium supplementation, alone or combined, for the primary prevention of fractures in men and premenopausal women.	I
Postmenopausal women	The USPSTF concludes that the current evidence is insufficient to assess the balance of the benefits and harms of daily supplementation with doses greater than 400 IU of vitamin D and greater than 1000 mg of calcium for the primary prevention of fractures in community-dwelling, postmenopausal women.	I
Postmenopausal women	The USPSTF recommends against daily supplementation with 400 IU or less of vitamin D and 1000 mg or less of calcium for the primary prevention of fractures in community-dwelling, postmenopausal women.	D

Read the Full Recommendation Statement

Supporting Documents

- Final Research Plan
- Final Evidence Review PDF Version (PDF Help)
- Evidence Summary PDF Version (PDF Help)

Clinical Summary

Clinical summaries are one-page documents that provide guidance to primary care clinicians for using recommendations in practice.

This summary is intended for use by

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