Korean Society for Health Promotion and Disease Prevention

2020년 대한임상건강증진학회 동계학술대회

2020. 12. 6 (일)

파이토뉴트리언트 등 건강기능식품과 이상지질혈증/심혈관질환 예방

명 승 권 (국립암센터)

파이토뉴트리언트란?

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파이토뉴트리언트(식물영양소)

▪ **Phytonutrients or phytochemicals**

- phyto (= plant, 식물)
- bioactive nutrient plant chemicals in fruits, vegetables, grains, and other plant foods that may provide desirable health benefits beyond basic nutrition to reduce the risk of major chronic diseases (Liu, 2004).
- 주로 과일과 채소에 풍부하며 기타 곡물, 견과류, 콩류, 차 등에도 존재
- 비타민이나 무기질처럼 생명유지에 필수는 아니지만 질병의 예방과 치료에 중요한 역할의 가능성 제기.
- 약 25,000 종 이상의 파이토뉴트리언트가 식물성 식품에서 발견.

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파이토뉴트리언트(식물영양소)

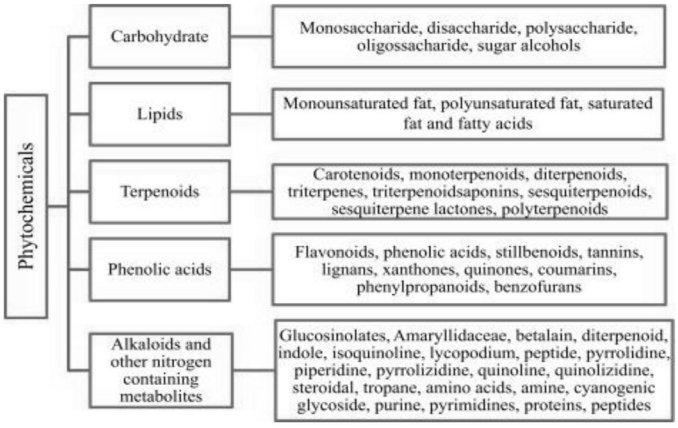

Figure 1. Categorization of phytochemicals. Harborne and Baxter, 1993; Campos-Vega and Oomah, 2013. *in Reference Module in Food Science 2016.*

파이토뉴트리언트(식물영양소)

▪ 대표적인 **파이토뉴트리언트**

1) 카로티노이드(Carotenoids)

- 노란색, 오렌지색, 붉은색을 띄며 과일과 채소에 600종 이상, 주로 항산화제 역할.
- **알파카로틴, 베타카로틴**: 비타민A로 전환, 호박 및 당근에 풍부
- **라이코핀:** 붉은색, 토마토, 수박 등
- **루테인/지아잔틴:** 백내장 및 황반변성에 도움, 시금치/케일 등.

2) 플라보노이드(Flavonoids)

- **카테킨**: 녹차
- **플라보놀(쿼세틴, quercetin):** 사과, 양파, 케일 등.

3) 레스베라트롤(Resveratrol: stilbenoid): 포도, 적포도주

4) 파이토에스트로젠(Phytoestrogen)

- **이소플라본**: 콩식품

건강기능식품이란?

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건강기능식품 생산실적 현황

- 건강기능식품 생산실적 현황(상위 5개 품목)

(단위 : 억원, %)

	17년 생산실적	생산액	점유율[1]		18년 생산실적	생산액	점유율[1]
1	홍삼	5,261	35.5	1	홍삼	6,765	39.1
2	개별인정형[2]	2,216	15.0	2	개별인정원료	2,453	14.2
3	비타민 및 무기질	1,901	12.8	3	비타민 및 무기질	2,136	12.4
4	프로바이오틱스	1,495	10.1	4	프로바이오틱스	1,898	11.0
5	밀크씨슬(카르두스 마리아누스) 추출물	739	5.0	5	EPA 및 DHA 함유 유지	536	3.1
	소계(상위 5개)	11,611	78.4		소계(상위 5개)	13,788	79.8

주1) 건강기능식품 생산액 중 점유율 현황을 의미함
주2) 영업자가 기준·규격, 안전성 및 기능성 등에 관한 자료를 제출하여 식품의약품안전처장으로부터 인정받은 제품을 말한다.

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출처: 식품의약품안전처, 2019년 8월 26일 발표.

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건강기능식품 시장 규모

- **국내의약품 생산실적**
  - **2018년 21조 1054억원(식품의약품안전처)**
- **국내 건강기능식품 생산실적(2019년 8월 26일 발표)**
  - **2018년 1조 7288억원(식품의약품안전처)**

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건강기능식품 출현 배경

- **Let food be thy medicine and medicine be thy food!**
  - 음식은 약이 되고 약은 음식이 되게 하라.
  - 히포크라테스가 한 말이라고 전해지나 출처 없음.
- **'의식동원(醫食同原)' 혹은 '약식동원(藥食同原)' – 중국, 한국**
  - 의약품이나 일상적으로 먹는 음식은 모두 인간의 생명을 유지하는데 필수적으로 근원이 같다.
- **누구나 잘 아는 건강하게 사는 법**
  - 금연, 절주, 운동, 표준 체중유지, 비타민/항산화물질/그 외 각종 영양물질이 풍부한 과일과 채소를 골고루 섭취하기.

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건강기능식품 출현 배경

▪ **음식에 풍부한 비타민/항산화제/영양물질은 질병을 예방한다!**

- 1950년대 이후 역학연구(집단 대상 질병의 인과관계 밝히는 연구방법) 수백 편을 종합하면, 과일과 채소를 골고루 자주 먹는 사람은 그렇지 않은 사람들보다 암, 심혈관질환 등 각종 질병이 적음.

***세계보건기구(WHO), 미국 CDC 및 여러 나라 국가캠페인**

건강을 위해 다양한 과일과 채소를 하루에 400g 이상 먹자.

하루에 5 가지 색깔이 다른 과일과 채소를 5 단위 먹자.

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5 A DAY 캠페인

▪ 세계보건기구와 서양 각국에서는 하루에 5가지 색깔(빨간색, 녹색, 노란색, 보라색, 하얀색)의 과일과 채소를 5 단위(400g = 2컵 반) 먹자는 5 A Day 캠페인 벌이고 있음.

▪ 다른 색깔마다 다른 비타민/항산화제/영양물질이 있음.

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건강기능식품 출현 배경

- **힘들고 귀찮으니, 그냥 건강기능식품을 먹자!**
  - 홍삼, 비타민, 오메가-3, 유산균, 글루코사민, 백수오, 프로폴리스, 스쿠알렌 등.
  - 수 십년 전부터 천연 비타민, 항산화물질 그리고 다양한 영양 물질을 음식에서 추출하거나 화학적 구조가 같은 물질을 합성하여 음식에 첨가하거나 해당 물질만 단독으로 보충제의 형태로 제조해 판매하기 시작 (종합비타민제 등).
  - 화학적 구조가 같다면 기능도 같을 것이라는 전제 하에.
  - '**건강기능식품**'이니 건강에 도움이 되는 기능을 갖고 있는데 약이 아닌 식품이라 부작용도 없을 것 같기도 하면서 알약이나 캡슐 등으로 되어 있어 간편하게 복용할 수 있겠지!
  - 외국: **펑셔널푸드(functional food), 뉴트라슈티컬(nutraceutical)**

건강기능식품이란? (우리나라)

- **2002년 8월, [건강기능식품에 관한 법률] 공포, 2004년 시행**
  - 건강기능식품의 안전성과 기능성을 평가 및 유통질서 관리목적
  - 제조·수입·판매에 대한 허가제와 신고제
  - 제조 등에 관한 기준과 규격, 위반행위 벌칙 등에 관한 규정.

- **건강기능식품의 정의(식약처 건강기능식품 홈페이지)**
  - 일상 식사에서 결핍되기 쉬운 **영양소**나 인체에 **유용한 기능성을 가진 원료나 성분**을 사용하여 **정제・캡슐・분말・과립・액상・환 등의 형태로 제조・가공한 식품으로 건강을 유지하는데 도움을 주는 식품**.
  - 식약처는 **동물시험, 인체적용시험 등 과학적 근거를 평가**하여 기능성원료를 인정하고 있음.

파이토뉴트리언트를 포함한 건강기능식품의 효능 평가와 근거중심의학의 필요성

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민간요법/건강기능식품/약/치료/처치가 효능이 있다는 것을 과학적/의학적으로 어떻게 증명할 수 있을까?

- 벌에 쏘였을 때 된장을 바르면 효과있다?
- 체했을 때 손 따면 증상이 가라앉는다?
- 비타민C 먹으면 감기에 덜 걸리거나 잘 낫는다?
- 홍삼을 먹으면 피로가 덜 하고 체력이 향상된다?
- 한약을 먹으면 힘이 난다?
- 커피 많이 먹으면 콜레스테롤 높아질까?
- 비타민C 주사 맞으면 피로가 덜 하다?

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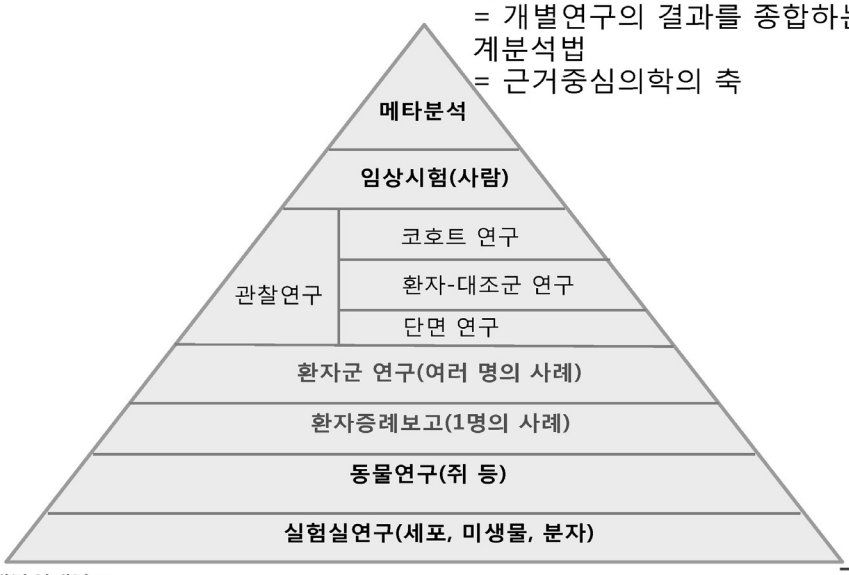
일반적인 질병치료와 관련한 특징

- 시간이 지나면 저절로 좋아짐(self-limited disease)
- 약리학적 효과가 없는 물질을 먹더라도 일부에서는 심리적 안정을 통해 질병이 낫기도 함(위약효과, placebo effect)
- 관심을 갖고 있는 A라는 요법이 아닌 B 등 다른 요인이 치료효과를 보였을 수 있음.

근거수준 피라미드(근거중심의학)

메타분석(Meta-analysis)
= 개별연구의 결과를 종합하는 통계분석법
= 근거중심의학의 축



특정 치료방법이 효능이 있다라고 이야기 하기 위해서는

- 몇 몇 환자의 경험이나 사례는 효능에 대한 인과관계를 확인할 수 없기 때문에
- 실험실 연구(세포, 미생물, 생물학적 분자 등) 및 동물연구(쥐 등)를 통해 효능 및 의학적 기전이 확인이 되고,
- 환자 즉 사람을 대상으로 한 무작위 '비교' 임상시험을 통해 효능 뿐 만 아니라 안전성이 입증이 되어야 함.
- 그럼에도 불구하고 파이토뉴트리언트를 포함해 현재 시판되고 있는 건강기능식품들은 비임상시험이나 소수의 임상시험을 근거로 그 기능성이나 효능이 허위 과장 광고되고 있음.
- 근거중심의학에 입각해 최근까지의 임상시험 및 임상시험을 종합한 메타분석을 바탕으로 파이토뉴트리언트를 포함한 건강기능식품의 효능에 대해 고찰하고자 함.

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라이코핀과 이상지질혈증/심혈관질환

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라이코핀

- **라이코핀(lycopene)**
  - 카로티노이드의 일종으로 토마토, 수박, 포도, 파파야 등에 풍부
  - 강력한 항산화제로 심혈관질환 예방에 도움이 될 수 있다는 가설 제기됨.

- **근거**

- 2017, Song et al, Mol Nutr Food Res: 14편의 관찰역학연구 메타분석 결과 라이코핀이 풍부한 음식을 섭취하는 경우 Coronary Heart Disease (RR = 0.87: 95% CI = 0.76-0.98) 및 Stroke (RR = 0.83; 95% CI = 0.42-0.87)가 유의하게 감소.

- 2011, Ried et al, Maturitas: 12편의 임상시험 메타분석 결과 하루 25 mg 이상의 라이코핀 복용은 LDL – Chol을 약 10% 감소시킴. 4편의 임상시험 메타분석결과 라이코핀은 수축기혈압을 5.6 mmHg 감소.

- 하지만, 라이코핀 보충제와 심혈관질환의 위험 관련성에 대한 임상시험의 메타분석은 발표되지 않음.

쿼세틴과 이상지질혈증/심혈관질환

쿼세틴

- **쿼세틴(quercetin)**
  - 플라보니이드의 일종인 식물플라보놀.
  - 여러가지 과일과 채소, 양파, 케일, 와인, 차 등에 풍부
  - 항산화 및 항염증 작용, lipid peroxidation 억제, pro-inflammatory cytokines expression 약화 등 다양한 기전을 통해 심혈관질환 예방에 도움이 될 수 있다는 가설 제기됨.

쿼세틴 보충제의 lipid profile 에 대한 효과

CRITICAL REVIEWS IN FOOD SCIENCE AND NUTRITION
2017, VOL. 57, NO. 4, 666–676
http://dx.doi.org/10.1080/10408398.2014.948609
Taylor & Francis

Effects of quercetin supplementation on lipid profile: A systematic review and meta-analysis of randomized controlled trials

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ABSTRACT

Background: In spite of promising experimental findings, randomized controlled trials (RCTs) have yielded mixed results on the impact of quercetin supplementation on plasma lipid levels.
Aim: The present study aimed to quantify the effects of quercetin on plasma lipids using a meta-analysis of RCTs.
Methods: A systematic literature search of Medline was conducted for RCTs that investigated the efficacy of quercetin supplementation on plasma lipids comprising total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglycerides. Weighted mean differences (WMDs) and 95% confidence intervals (CIs) were calculated for net changes in lipid concentrations using a random-effects model. Meta-regression analysis was conducted to assess the effect of quercetin dose and duration of supplementation as moderators on the calculated effect measures.
Results: Five RCTs totaling 442 subjects (221 in the quercetin and 221 in the control group) fulfilled the eligibility criteria and selected for analyses. Combined estimate of effect size for the impact of quercetin on plasma LDL-C (WMD: 1.43 mg/dL, 95% CI: −0.92–3.78, $p = 0.23$), HDL-C (WMD: 0.26 mg/dL, 95% CI: −0.74–1.25, $p = 0.61$) and triglycerides (WMD: −9.42 mg/dL, 95% CI: −27.80–8.96, $p = 0.32$) was not statistically significant. However, a borderline significant but clinically non-relevant increase in total cholesterol was observed (WMD: 3.13 mg/dL, 95% CI: −0.01–6.27, $p = 0.05$). When the analysis was confined to the subgroups of studies with quercetin doses ≥500 mg/day and follow-up of ≥ 4 weeks, a significant increase in total cholesterol (WMD: 3.57 mg/dL, 95% CI: 0.21–6.92, $p = 0.04$) and a decline in triglycerides (WMD: −24.54 mg/dL, 95% CI: −33.09 to −15.99, $p < 0.00001$) was observed, but LDL-C and HDL-C concentrations remained unchanged ($p > 0.05$). Changes in plasma triglycerides, but not other indices of lipid profile, were significantly associated with quercetin dose (slope: −0.057; 95% CI: −0.103 to −0.010) $p = 0.02$) and duration of supplementation (slope: −5.314; 95% CI: −9.482 to −1.147; $p = 0.01$).
Conclusion: Available evidence from RCTs does not suggest any clinically relevant effect of quercetin supplementation on plasma lipids, apart from a significant reduction of triglycerides at doses above 50 mg/day.

Abbreviations: ACVD: Atherosclerotic cardiovascular disease; BMI: Body mass index; CI: Confidence interval; CMA: Comprehensive meta-analysis; HDL-C: High-density lipoprotein cholesterol; HOMA-IR: Homeostasis model assessment-estimated insulin resistance; LDL-C: Low-density lipoprotein cholesterol; SD: Standard deviation; SEM: Standard error of the mean; WMD: Weighed mean difference

KEYWORDS
Flavonoid; polyphenol; systematic review; dyslipidemia; cardiovascular disease

Introduction

Accumulating evidence over the past decades has shown that circulating lipid concentrations is a major determinant of the risk of atherosclerotic cardiovascular disease (ACVD) (Egert et al., 2008; Rizzo et al., 2013; Banach et al., 2014). Dyslipidemia is a leading, yet modifiable, risk factor for ACVD that is characterized by increased plasma levels of low-density lipoprotein cholesterol (LDL-C) and/or triglycerides, and/or diminished levels of high-density lipoprotein cholesterol (HDL-C). Although several classes of lipid-modifying agents are available, the efficacy of such agents to achieve optimal lipid targets is limited (Kelly, 2011). Besides, there are safety concerns associated with the use of statins and fibrates, as the most widely used hypolipidemic drugs, due to the incidence of adverse effects such as myopathy and hepatotoxicity (Nutrient Data Laboratory, Food Composition Laboratory. 2007; Michalska et al., 2010). Given these drawbacks, there has been a surge of interest to find new agents with lipid-modifying properties to be used as adjuncts to low-dose statins in patients who cannot tolerate higher doses (Graefe et al., 1999; Hollman and Katan, 1999; Gee et al., 2000; Ying et al., 2013; Gnoni et al., 2009). Natural products with lipid-modifying properties often possess several pleiotropic properties important for the proper functioning of CV system and have greater safety compared to

- 5편의 RCT(442 명)를 메타분석
- 쿼세틴 보충제는 혈장 LDC-chol, HDL-Chol 및 TG 에 통계적으로 유의한 효과 관찰되지 않음.
- 500 mg/d 이상의 용량에서 Total Chol은 증가하고 TG는 감소했음.

Sahebkar, Crit Rev Food Sci Nutr, 2017.

쿼세틴 보충제의 lipid profile 에 대한 효과

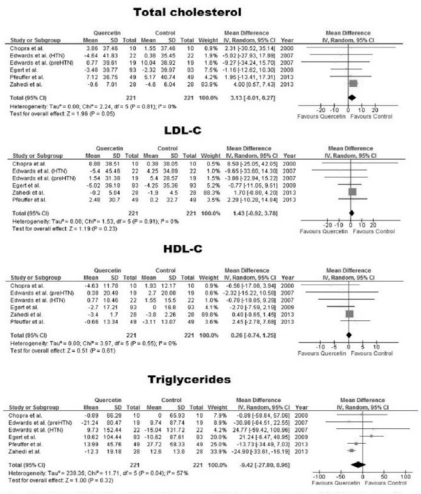


Figure 2. Forest plot detailing weighted mean difference and 95% confidence intervals for the impact of quercetin supplementation on plasma lipids.

Sahebkar, Crit Rev Food Sci Nutr, 2017.

레스베라트롤과 이상지질혈증/심혈관질환

레스베라트롤

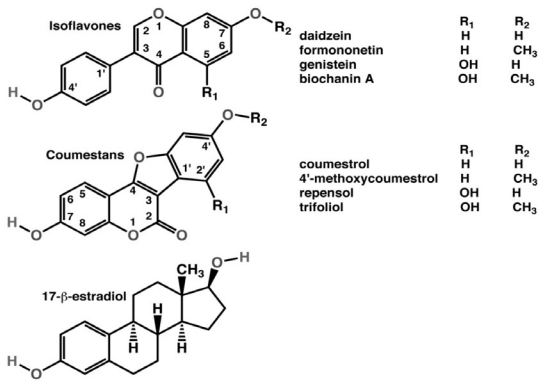
- **레스베라트롤(resveratrol)**
  - 폴리페놀의 일종인 스틸베노이드(stilbenoid).
  - 포도, 블루베리, 라스베리 등에 풍부
  - 항산화제로 산화적 스트레스, 안지오텐신2 등을 감소시켜 혈압강하 효과가 제기됨.

- **근거**
  - 2015, Liu et al, Clin Nutr: 6편의 임상시험(247명)을 메타분석, 고용량에서 수축기 혈압을 감소시키나 확장기 혈압에는 유의한 효과 관찰되지 않음.

  - 2019, Asgary et al, Rev Endocr Metab Disord: 10편의 임상시험 메타분석, 혈당 및 허리둘레는 감소, 수축기혈압 및 총콜레스테롤/중성지방/고밀도콜레스테롤에는 유의한 효과없음.

파이토에스트로젠과 이상지질혈증/심혈관질환

파이토에스트로젠



▪ **파이토에스트로젠 (Phytoestrogens)**

- 식물성 에스트로젠
- 대두 및 콩과류, 참깨 등에 풍부
- 심혈관질환, 유방암, 폐경기 증후군 등에 효과적이라는 가설이 제기됨.
- 파이토에스트로젠을 함유한 음식의 섭취는 심혈관질환의 위험성을 낮춘다는 전향적 코호트 연구의 메타분석 결과는 다수 발표되었지만, 임상시험을 종합한 메타분석은 없음.

제니스틴 보충제의 고혈압에 대한 효과에 대한 가능한 기전

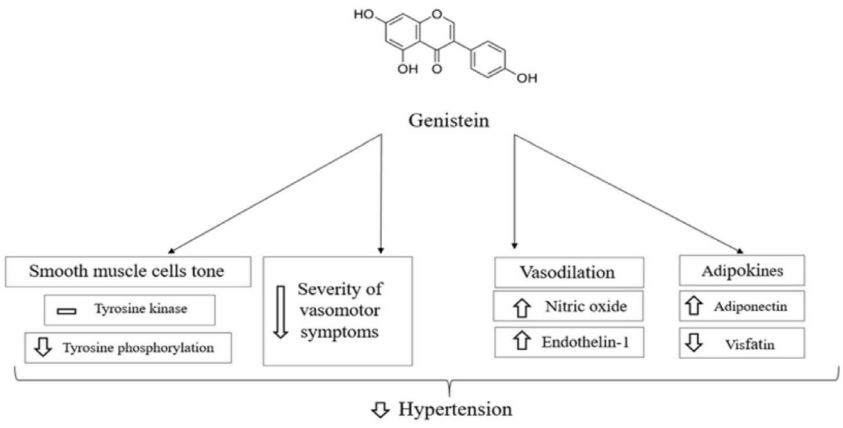


Fig. 6. An overview of various possible mechanisms involved in the effect of genistein on hypertension.

Hemati et al, Food Res Int, 2020.

콩 및 이소플라본 섭취와 건강

REVIEW

Molecular Nutrition & Food Research

www.mnf-journal.com

Soy and Isoflavone Consumption and Multiple Health Outcomes: Umbrella Review of Systematic Reviews and Meta-Analyses of Observational Studies and Randomized Trials in Humans

*Ni Li, Xiaoting Wu, Wen Zhuang, Lin Xia, Yi Chen, Rui Zhao, Mengshi Yi, Qianyi Wan, Liang Du, and Yong Zhou**

Scope: To assess the existing evidence of associations between consumption of soy and isoflavone and multiple health outcomes.
Methods and results: This is an umbrella review of meta-analyses and systematic reviews of randomized trials and observational studies in humans. 114 Meta-analyses and systematic reviews are identified with 43 unique outcomes. Soy and isoflavone consumption seems more beneficial than harmful for a series of health outcomes. Beneficial associations are identified for cancers, cardiovascular disease, gynecological, metabolic, musculoskeletal, endocrine, neurological, and renal outcomes, particularly in perimenopausal women. Harmful association is only found for gastric cancer (RR: 1.17, 95% CI: 1.02–1.36) for high intake of miso soup (1–5 cups per day) in male.
Conclusion: Generally, soy and isoflavone consumption is more beneficial than harmful. The results herein support promoting soy intake as part of a healthy diet. Randomized controlled trials are necessary to confirm this finding.

1. Introduction

Soybean (*Glycine max*), which was first domesticated in the Northeastern China around 1100 B.C.,[1] is one of the most important crop plants for seed protein and oil content, and for its capacity to fix atmospheric nitrogen through symbioses with soil-borne microorganisms.[2] It is a rich source of bioactive compounds, some with potentially therapeutic antihyperlipidemic,[3] antithyroglycaemic,[4] antihypertensive,[5] antioxidant,[6] anti-inflammatory,[7] anticancer,[8] antiobesity,[9] and neuroprotective[10] activities that support the biological plausibility for observational associations. As key active compounds, isoflavones (genistein, daidzein, and glycitein) are changed in the body to phytoestrogens, which are bioactive compounds with mildly estrogenic properties.[11] Although processed soy food products (such as soy milk, tofu, miso, natto) have been an integral part of regular diets in Asia (e.g., China, Japan, and Korea) for centuries, the consumption of this food in the West is recent.[12] Evidence from clinical trials show that the consumption of soy protein decreases serum cholesterol concentrations in humans.[13] Accordingly, the U.S. Food and Drug Administration (FDA) authorized the use on food labels of health claims associated with soy protein and the reduced risk of coronary heart disease by lowering blood cholesterol levels.[14]

Recent epidemiological studies have explored the associations between consumption of soy and isoflavone and a wide series of outcomes (including mortality, cancers, cardiovascular disease, gynecological, metabolic, musculoskeletal, endocrine, neurological, and renal outcomes).[15] Most of these studies were not interventional in design, dependent on evidence from cohort, case-control or cross-sectional studies and frequently generalized by outcome through meta-analysis and systematic review. There have been conflicting conclusions if soy and isoflavone consumption is good or damaging to health, and the roles of soy and isoflavone were different among various health outcomes.[16] Newly discovered associations often have inflated effects compared with the true effects.[17] Inherent biases in study, for example, reporting bias and residual confounding may overinflate the magnitudes of the observed effects.[17] Both randomized controlled trials (RCTs) and observational studies have strengths and weaknesses, and including information from observational studies, may improve the inference based on only RCTs.[18]

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- 무작위 임상시험 및 관찰연구를 종합한 114 편의 메타분석 및 체계적 문헌고찰을 고찰(umbrella review)
- 전반적으로 콩 및 이소플라본 섭취는 심혈관질환을 포함해 다양한 질병과 관련해 해로움보다는 이득이 큼.
- 하지만, 무작위 비교임상시험을 통해 확인이 필요함.

Li et al, Mol Nutr Food Res, 2020.

콩 및 이소플라본 섭취와 건강

Table 2. Associations between soy and isoflavone consumption and mortality and cardiovascular disease.

Outcome	Category	Study	No. of cases/total	MA metric	Estimates	95% CI	No. of studies in MA	Cohort	Case control	RCT	Effects model	I^2 [%]	Egger test *p*-value
Mortality													
Significant associations													
CVD mortality	FS	[24]	1910/69 529	RR[a]	0.84	0.73–0.97	3	3	0	0	Random	0.0	NA
Non-significant associations													
All-causes mortality	Soy	[24]	18 992/141 335	RR[b]	0.96	0.90–1.02	3	3	0	0	Random	38.5	0.86
CVD mortality	Soy	[24]	6028/140 893	RR[b]	0.95	0.82–1.10	4	4	0	0	Random	49.9	0.40
Cancer mortality	Soy	[24]	12 802/144 490	RR[b]	0.98	0.92–1.05	4	4	0	0	Random	0.0	0.46
Cardiovascular outcomes													
Significant associations													
CVD	Soy	[33]	17 269/492 676	RR[b]	0.83	0.75–0.93	17	10	7	0	Random	71.4	0.02
Stroke	Soy	[33]	6265/373 928	RR[b]	0.82	0.68–0.99	11	7	4	0	Random	78.8	0.01
Coronary heart disease	Soy	[33]	10 806/441 140	RR[b]	0.83	0.72–0.95	12	8	4	0	Random	64.6	0.30
Endothelial function	Iso	[34]	1281#	ME[c]	1.98%	0.07–3.97	17	0	0	17	Bayesian	NA	NA
Systolic blood pressure	Soy	[35]	1551#	WMD[d]	−4.62 mmHg	−8.42, −0.81	12	0	0	12	Random	69.2	0.51
Diastolic blood pressure	Soy	[35]	1551#	WMD[d]	−1.63 mmHg	−2.85, −0.41	12	0	0	12	Random	25.1	0.17
Systolic blood pressure	Iso	[35]	1551#	WMD[d]	−5.47 mmHg	−8.42, −2.51	12	0	0	12	Random	54.5	0.51
Diastolic blood pressure	Iso	[35]	1551#	WMD[d]	−2.03 mmHg	−3.35, −0.72	12	0	0	12	Random	0.0	0.17
LDL cholesterol	Soy	[36]	1687/1679*	WMD[c]	−4.83 mg dL^{-1}	−7.34, −2.31	35	0	0	35	Random	97.0	NA
HDL cholesterol	Soy	[36]	1659/1651*	WMD[c]	1.40 mg dL^{-1}	0.58, 2.23	35	0	0	35	Random	95.0	NA
TC	Soy	[36]	1630/1617*	WMD[c]	−5.33 mg dL^{-1}	−8.35, −2.30	35	0	0	35	Random	99.0	NA
TAG	Soy	[36]	1502/1496*	WMD[c]	−4.92 mg dL^{-1}	−7.79, −2.04	35	0	0	35	Random	92.0	NA
Plasma lipoprotein(a)	Iso	[37]	489/484*	SMD[c]	0.08	−0.05, 0.20	10	0	0	10	Random	0.0	0.63
Non-significant associations													
CVD	Iso	[33]	10 766/375 830	RR[b]	0.98	0.88–1.10	8	8	0	0	Random	63.3	NA
Stroke	Iso	[33]	6184/319 674	RR[b]	1.00	0.81–1.23	6	6	0	0	Random	76.0	NA
Coronary heart disease	Iso	[33]	6669/308 998	RR[b]	0.96	0.86–1.07	7	7	0	0	Random	27.1	NA
Endothelial function	Soy	[34]	1281#	ME[c]	0.72%	−1.39, 2.90	17	0	0	17	Bayesian	NA	NA

MA, meta-analysis; CI, confidence interval; RCT, randomized controlled trial; FS, fermented soy; Iso, isoflavones; RR, relative risk; OR, odds ratio; SMD, standardized mean difference; WMD, weighted mean difference; ME, mean estimate; NA, not available; CVD, cardiovascular disease; TAG, triglyceride; TC, total cholesterol. [a]not available; [b]highest versus lowest/none; [c]any versus none; [d]25 g per day versus none; [e]100 mg per day versus none. *cases/control; #participants.

- **콩 및 이소플라본 섭취가 혈압 및 지질(LDL 등)에 대해 긍정적인 효과를 보인 메타분석이 여러 편 발표됨.**
- **하지만, 심혈관질환(CVD) 질환 사망률이나 발생에 대한 임상시험의 메타분석은 없음.**
- **통계적 유의성은 있지만 임상적 유의성은 적어 보임.**

Li et al, Mol Nutr Food Res, 2020.

우리나라 건강기능식품제도의 문제점

건강기능식품의 문제점(1) – 비과학적인 정의

▪ 질병의 예방과 치료없이 건강을 유지하고 개선한다는 것은 비과학적이며 성립될 수 없는 비논리적 개념.

▪ 뉴트라슈티컬: neutraceutical: nutrition (영양) + pharmaceutical (약)
'질병을 예방하거나 치료하는 것을 포함해 의학적 혹은 건강상의 이득을 줄 수 있는 음식(혹은 음식의 일부분)으로 정의할 수 있다' – 미국 스티븐 디펠리스.

건강기능식품의 문제점(2) – 허술한 기능성 등급

생리활성기능은 과학적 근거 정도에 따라 3가지 등급으로 구분된다.

기능성 등급		기능성 내용	인정 기준
질병발생위험 감소기능		○○발생위험 감소에 도움을 줌	기반연구자료를 통해 생리학적인 효과 또는 기전이 명확하게 입증되어야 하고 일관성 있는 바이오마커의 개선효과가 다수의 인체적용시험(RCT)에서 확보되어야 함 * 질병 관련 바이오마커의 확인
생리활성기능	1등급	○○에 도움을 줌	기반연구자료를 통해 생리학적인 효과 또는 기전이 명확하게 입증되어야 하고 일관성 있는 바이오마커의 개선효과가 다수의 인체적용시험(RCT)에서 확보되어야 함 * 생리활성 관련 바이오마커의 확인
	2등급	○○에 도움을 줄 수 있음	기반연구자료를 통해 가능성 있는 생리학적인 효과 또는 기전을 추측할 수 있어야 하고 일관성 있는 바이오마커의 개선효과가 최소 1건 이상의 인체적용시험(RCT)에서 확보되어야 함 (추측 제안기전과 관련한 바이오마커 1개라도 기반연구시험과 인체적용시험에서 일관성 있게 확인되어야 함) * 생리활성 관련 바이오마커의 확인
	3등급	○○에 도움을 줄 수 있으나 관련 인체적용시험이 미흡함	기반연구자료를 통해 생리학적인 효과 또는 기전을 추측할 수 있는 자료가 있으나, 인체적용시험(RCT)에서 기능성을 확보할 수 없음

▪ 질병발생위험 감소기능: 질병예방에 해당하므로 의약품으로 분류해야 함.

▪ 생리활성 기능 2등급: 임상시험 1 편만 있어도 기능성을 인정해주는 것은 심각한 근거불충분. 없애야 함.

▪ 생리활성 기능 3등급: 실험실연구나 동물실험에서만 기능성이 추측되며 임상시험은 없음. 없애야 함.

건강기능식품의 문제점(2) – 허술한 기능성 등급

▪ **총 230여종의 건강기능식품 중 기능성 등급별 갯수와 종류**

1) 질병발생위험 감소기능

- **3종**. 칼슘/비타민D(골다공증), 자일리톨(충치)

2) 생리활성기능 1등급

- **7종**. 글루코사민, 대두이소플라본, 루테인, 지아잔틴, 가르시니아캄보지아, 폴리감마글루탐산, 폴리코사놀.

3) 생리활성기능 2등급(임상시험 최소 1편 이상) 및 **3 등급**(임상시험 없어도)

- **약 220종.** 대부분은 홍삼, 백수오, 비타민, 오메가3, 유산균 등 2등급, 수십종은 3등급.

칼슘 보충제와 심혈관질환

칼슘보충제와 심근경색증

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,[4] Greg D Gamble, research fellow,[1] Ian R Reid, professor[1]

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Cite this as: BMJ 2010;341:c3691
doi:10.1136/bmj.c3691

ABSTRACT

Objective To investigate whether calcium supplements increase the risk of cardiovascular events.

Design Patient level and trial level meta-analyses.

Data sources Medline, Embase, and Cochrane Central Register of Controlled Trials (1966-March 2010), reference lists of meta-analyses of calcium supplements, and two clinical trial registries. Initial searches were carried out in November 2007, with electronic database searches repeated in March 2010.

Study selection Eligible studies were randomised, placebo controlled trials of calcium supplements (≥500 mg/day), with 100 or more participants of mean age more than 40 years and study duration more than one year. The lead authors of eligible trials supplied data. Cardiovascular outcomes were obtained from self reports, hospital admissions, and death certificates.

Results 15 trials were eligible for inclusion, five with patient level data (8151 participants, median follow-up 5.6 years, interquartile range 2.7-6.3 years) and 11 with trial level data (11 921 participants, mean duration 4.0 years). In the five studies contributing patient level data, 143 people allocated to calcium had a myocardial infarction compared with 111 allocated to placebo (hazard ratio 1.31, 95% confidence interval 1.02 to 1.67, P=0.035). Non-significant increases occurred in the incidence of stroke (1.20, 0.96 to 1.50, P=0.11), the composite end point of myocardial infarction, stroke, or sudden death (1.18, 1.00 to 1.39, P=0.057), and death (1.09, 0.96 to 1.23, P=0.18). The meta-analysis of trial level data showed similar results: 296 people had a myocardial infarction (166 allocated to calcium, 130 to placebo), with an increased incidence of myocardial infarction in those allocated to calcium (pooled relative risk 1.27, 95% confidence interval 1.01 to 1.59, P=0.038).

Conclusions Calcium supplements (without coadministered vitamin D) are associated with an increased risk of myocardial infarction. As calcium supplements are widely used these modest increases in risk of cardiovascular disease might translate into a large burden of disease in the population. A reassessment of the role of calcium supplements in the management of osteoporosis is warranted.

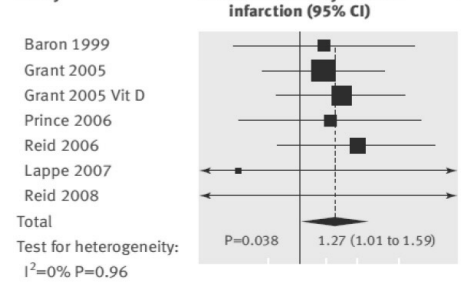
INTRODUCTION

Osteoporosis is a major cause of morbidity and mortality in older people.[1] Calcium supplements marginally reduce the risk of fracture,[2-5] and most guidelines recommend adequate calcium intake as an integral part of the prevention or treatment of osteoporosis.[6-8] Consequently, calcium supplements are commonly used by people over the age of 50. Observational studies suggest that high calcium intake might protect against vascular disease,[9-14] and the findings are consistent with those of interventional studies of calcium supplements that show improvement in some vascular risk factors.[15-17] In contrast, calcium supplements accelerate vascular calcification and increase mortality in patients with renal failure, in both dialysis and predialysis populations.[18-20] Furthermore, a five year randomised controlled trial of calcium supplements in healthy older women, in which cardiovascular events were prespecified as secondary end points, recently reported possible increases in rates of myocardial infarction and cardiovascular events in women allocated to calcium.[21-24] We carried out a meta-analysis of cardiovascular events in randomised trials of calcium supplements.

METHODS

In November 2007 we searched Medline, Embase, and the Cochrane Central Register of Controlled Trials for randomised placebo controlled trials of calcium supplements, using the terms "calcium", "randomised controlled trial", and "placebo" as text words, and corresponding MeSH terms (full details are available from the authors). We searched for studies in the reference lists of meta-analyses published between 1990 and 2007 of the effect of calcium supplements on bone density, fracture, colorectal neoplasia, and blood pressure, and in two clinical trial registries (ClinicalTrials.gov and Australian New Zealand Clinical Trials Registry). No language restrictions were applied. In March 2010 we updated the searches of the electronic databases (Medline: January 1966-March 2010, Embase: January 1980-March 2010, Central Register of Controlled Trials: first quarter 2010).

- **7편의 임상시험 메타분석**
  - 심근경색증의 위험성이 27% 높아짐



Bolland et al, British Medical Journal 2010

칼슘보충제와 심혈관질환

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

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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

- **7편 무작위비교임상시험(RCT) 메타분석**
  - 칼슘보충제와 심근경색증 간에 유의한 관련성 없음

a **Myocardial Infarction**

Study or Subgroup	Calcium Events	Calcium Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Grant 2005 (Ca)	26	1113	13	1128	4.7%	2.03 [1.05, 3.92]
Grant 2005 (CaD)	23	1104	18	1136	5.4%	1.31 [0.71, 2.42]
Jackson 2006	411	18176	390	18106	59.5%	1.05 [0.92, 1.20]
Lappe 2007	5	892	2	288	0.8%	0.81 [0.16, 4.14]
Larsen 2004	66	2983	72	2788	16.9%	0.86 [0.62, 1.19]
Prince 2006	21	769	20	730	5.6%	1.00 [0.54, 1.82]
Reid 2006	31	732	21	739	6.8%	1.49 [0.88, 2.57]
Sambrook 2012	1	139	3	288	0.4%	0.69 [0.07, 6.58]
Total (95% CI)		25908		25203	100.0%	1.08 [0.93, 1.25]
Total events	584		539			

Heterogeneity: Tau² = 0.00; Chi² = 7.58, df = 7 (P = 0.37); I² = 8%
Test for overall effect: Z = 1.00 (P = 0.32)

Risk Ratio M-H, Random, 95% CI
0.1 0.2 0.5 1 2 5 10
Favours calcium Favours placebo

Lewis et al, JBMR, 2015

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칼슘보충제와 심혈관질환

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; Zhuoxuan 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.

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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 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:
Related article 867
Editorial comment 884
Web-Only
Supplement

- **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

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칼슘보충제와 심혈관질환

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; Jeri 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 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.

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/not-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

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CME quiz

- 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

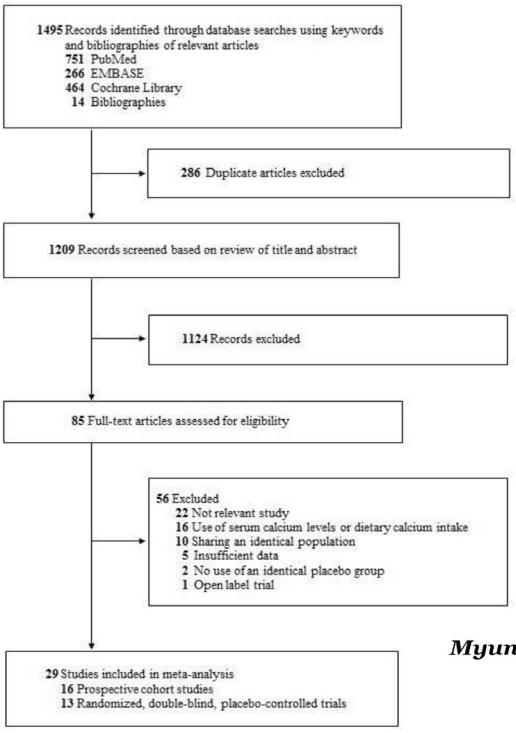
Myung et al, 2020: under review

- Those inconsistent findings are thought to be attributable to **different selection criteria** that were used in each meta-analysis, such as type of study, study population, and inclusion of unpublished data.

- We investigated the associations between **the use of calcium supplements and the risk of CVD** by conducting a comprehensive meta-analysis of prospective cohort studies and randomized, double-blind, placebo-controlled trials (RDBPCTs) with various subgroup analyses according to important factors that can affect the results.

Results

Figure 1. Study selection.



Myung et al, under review

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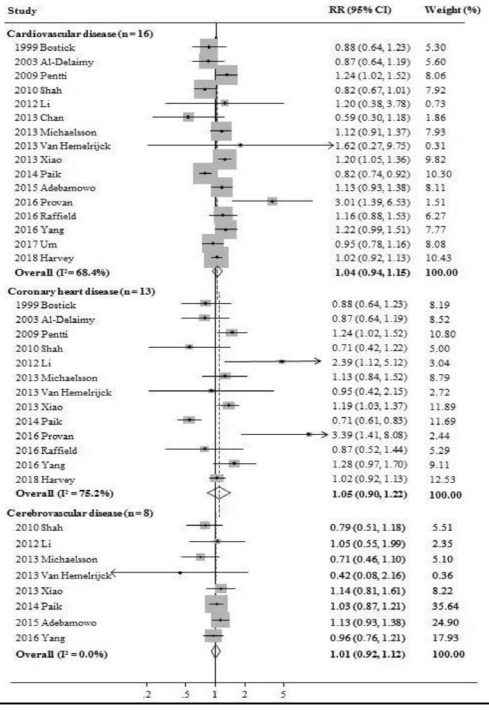
Figure 2. Use of Calcium Supplements and Risk of Cardiovascular Disease in a Random-effects Meta-analysis of Prospective Cohort Studies. RR, relative risk; CI, confidence interval.



Results

- **Meta-analysis of prospective cohort studies**
  - No significant association between calcium supplements and CVD/CHD/CrbVD.

Myung et al, under review

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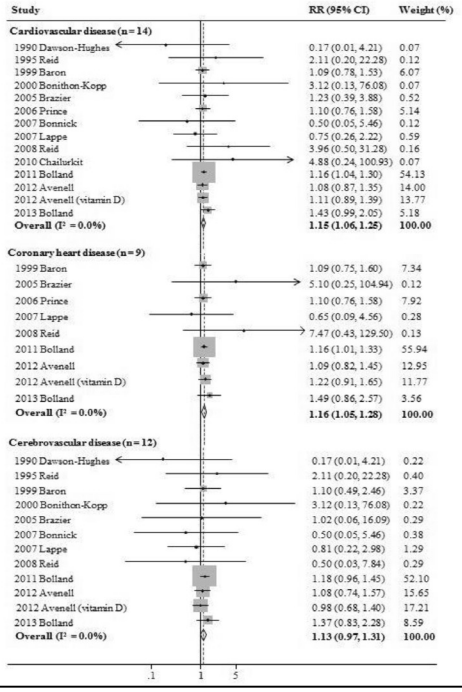
Figure 3. Use of Calcium Supplements and the Risk of Cardiovascular Disease in a Random-effects Meta-analysis of Randomized Controlled Trials. RR, relative risk; CI, confidence interval. Avenell et al's trial[42] used both calcium alone and calcium plus vitamin D in the supplementation groups. Thus, a total of 14 trials were included in the analysis.



Results

- **Meta-analysis of RDBPCTs**

An increased association between calcium supplements and CVD/CHD, not CrbVD.

- RR = 1.15 (95% CI, 1.06-1.25) for CVD

- RR = 1.16 (95% CI, 1.05-1.28) for CHD

Myung et al, under review

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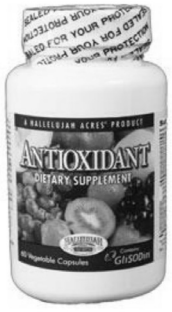

비타민/항산화보충제와 심혈관질환

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자유라디칼/활성산소종

▪ **자유라디칼**

짝짓지 않은 전자를 가지는 원자단으로 매우 불안정하여 수명이 수초 짧게는 수억분의 일초로 생기자 마자 다른 물질과 반응하여 전자를 빼앗아 세포에 손상을 줌.

▪ **활성산소종(Reactive Oxygen Species)**

- 정상 세포대사과정 중 영양분이 에너지로 바뀌는 과정에서 산소는 대부분 물을 형성하지만, 일부는 반응성이 높은 O_2^-, H_2O_2, OH 활성산소종이 생성(=유해산소). 인체의 대표적 자유라디칼.
- 생기자마자 정상 세포의 DNA나 세포막 **산화공격하여 암, 심혈관질환 발생 및 노화 촉진**.

*원인

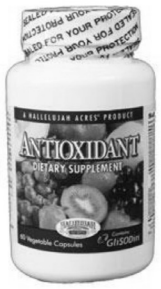
흡연, 공해, 태양자외선, 음식, 화학물질, 방사선 등에 의해 자유라디칼 혹은 활성산소종이 과다하게 생성.

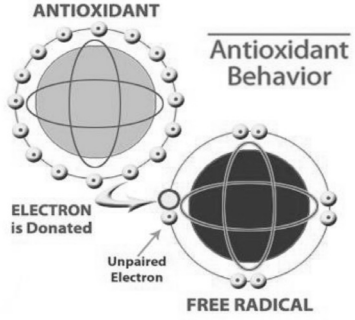
항산화제(Antioxidant)

▪ **역할**

다른 물질의 산화를 느리게 하거나 막아주는 물질로, 특히 활성산소종과 같은 자유라디칼에 의한 산화적 손상을 막아줌으로써 질병예방이 가능.

▪ **원천**: 과일과 채소, 항산화 보충제





음식에 들어 있는 천연 항산화제의 종류

- **비타민**
  비타민 C (감귤, 오렌지), 비타민 E(식물성 기름, 땅콩)

- **파이토케미칼(식물성화학물질)**
  가. 카로티노이드
  베타카로틴(비타민 A 전구물질/프로비타민; 당근, 시금치, 호박),
  라이코핀 (토마토, 수박)
  나. 이소플라본(콩류)
  다. 차 폴리페놀(녹차 카테킨)
  라. 레스베라트롤(적포도주)

- **무기질**
  셀레늄(Se 34; 어패류, 육류, 견과류)

비타민/항산화제와 사망률(2007, JAMA)

REVIEW

Mortality in Randomized Trials of Antioxidant Supplements for Primary and Secondary Prevention
Systematic Review and Meta-analysis

Goran Bjelakovic, MD, DrMedSci
Dimitrinka Nikolova, MA
Lise Lotte Gluud, MD, DrMedSci
Rosa G. Simonetti, MD
Christian Gluud, MD, DrMedSci

Context Antioxidant supplements are used for prevention of several diseases.

Objective To assess the effect of antioxidant supplements on mortality in randomized primary and secondary prevention trials.

Data Sources and Trial Selection We searched electronic databases and bibliographies published by October 2005. All randomized trials involving adults comparing beta carotene, vitamin A, vitamin C (ascorbic acid), vitamin E, and selenium either singly or combined vs placebo or vs no intervention were included in our analysis. Randomization, blinding, and follow-up were considered markers of bias in the included trials. The effect of antioxidant supplements on all-cause mortality was analyzed with random-effects meta-analyses and reported as relative risk (RR) with 95% confidence intervals (CIs). Meta-regression was used to assess the effect of covariates across the trials.

Data Extraction We included 68 randomized trials with 232 606 participants (385 publications).

Data Synthesis When all low- and high-bias risk trials of antioxidant supplements were pooled together there was no significant effect on mortality (RR, 1.02; 95% CI, 0.98-1.06). Multivariate meta-regression analyses showed that low-bias risk trials (RR, 1.16; 95% CI, 1.05-1.29) and selenium (RR, 0.998; 95% CI, 0.997-0.9995) were significantly associated with mortality. In 47 low-bias trials with 180 938 participants, the antioxidant supplements significantly increased mortality (RR, 1.05; 95% CI, 1.02-1.08). In low-bias risk trials, after exclusion of selenium trials, beta carotene (RR, 1.07; 95% CI, 1.02-1.11), vitamin A (RR, 1.16; 95% CI, 1.10-1.24), and vitamin E (RR, 1.04; 95% CI, 1.01-1.07), singly or combined, significantly increased mortality. Vitamin C and selenium had no significant effect on mortality.

Conclusions Treatment with beta carotene, vitamin A, and vitamin E may increase mortality. The potential roles of vitamin C and selenium on mortality need further study.

JAMA. 2007;297:842-857 www.jama.com

METHODS

The present review follows the Cochrane Collaboration method[17] and is based on the principles of our peer-reviewed protocol and review on antioxidant supplements for gastrointestinal cancer prevention.[14,15,18,19] We included all primary and secondary prevention trials in adults randomized to receive beta caro-

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- **2007년, Bjelakovic et al, 미국의 학협회지(JAMA)**

16년간 발표된 질적수준이 높은 (low-bias) **총 47편의 임상시험(총 18만 여명 대상)의 결과를 종합 '메타분석'**한 결과,

비타민 A, C, E, 베타카로틴, 셀레늄과 같은 비타민/항산화 보충제를 복용하는 경우 그렇지 않은 경우보다 **사망률이 오히려 5% 높음.**

← 상대위험도(RR), 1.05 (95% 신뢰구간: 1.02-1.08)

비타민/항산화보충제와 암예방(2010, Ann Oncol)

original article

Annals of Oncology 21: 166–179, 2010
doi:10.1093/annonc/mdp369
Published online 21 July 2009

Effects of antioxidant supplements on cancer prevention: meta-analysis of randomized controlled trials

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Received 15 September 2008; revised 21 January 2009 & 3 April 2009; accepted 20 April 2009

Background: The meta-analysis aimed to investigate the effect of antioxidant supplements on the primary and secondary prevention of cancer as reported by randomized controlled trials.
Methods: We searched Medline (PubMed), Excerpta Medica database, and the Cochrane Review in October 2007. **Results:** Among 3327 articles searched, 31 articles on 22 randomized controlled trials, which included 161 045 total subjects, 88 610 in antioxidant supplement groups and 72 435 in placebo or no-intervention groups, were included in the final analyses. In a fixed-effects meta-analysis of all 22 trials, antioxidant supplements were found to have no preventive effect on cancer [relative risk (RR) 0.99, 95% confidence interval (CI) 0.96–1.03]. Similar findings were observed in 12 studies on primary prevention trials (RR 1.00, 95% CI 0.97–1.04) and in nine studies on secondary prevention trials (RR 0.97, 95% CI 0.83–1.13). Further, subgroup analyses revealed no preventive effect on cancer according to type of antioxidant, type of cancer, or the methodological quality of the studies. On the other hand, the use of antioxidant supplements significantly increased the risk of bladder cancer (RR 1.52, 95% CI 1.06–2.17) in a subgroup meta-analysis of four trials.
Conclusions: The meta-analysis of randomized controlled trials indicated that there is no clinical evidence to support an overall primary and secondary preventive effect of antioxidant supplements on cancer. The effects of antioxidant supplements on human health, particularly in relation to cancer, should not be overemphasized because the use of those might be harmful for some cancer.
Key words: antioxidants, cancer, meta-analysis, prevention, randomized controlled trials

original article

introduction

Previous experimental studies using *in vivo* animal models and *in vitro* cancer cell lines have reported that antioxidants such as vitamins, beta-carotene, and selenium may reduce oxidative damage and prevent human diseases, including cancer [1–4]. Also, the previous 200 epidemiologic studies have indicated that persons with a low intake of fruits and vegetables that are rich in antioxidant substances are more susceptible to cancer [5].

However, a systematic review of randomized controlled trials published in 2006 reported that the currently available evidence was insufficient to prove whether or not multivitamin supplements were beneficial toward the prevention of cancer and chronic disease [6]. A recently published meta-analysis of 47 low-bias trials involving 180 938 participants revealed that compared with the control group, the antioxidant supplement group exhibited a mortality rate that was significantly higher by at least 5% [7]. A meta-analysis of randomized controlled trials also showed that antioxidant supplements do not exert any significant effects against the development of gastrointestinal cancers and that they increase all-cause mortality [8]. Recently, in a meta-analysis of 12 randomized clinical trials, Bardia et al. [9] reported that antioxidant supplementation did not significantly reduce total cancer incidence or mortality or any site-specific cancer incidence in participants who had neither history of cancer nor precancerous lesions (i.e. primary prevention only). Furthermore, according to the recent report from World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) published in 2007, the strongest evidence, corresponding to judgments of 'convincing' or 'probable', showed that high-dose beta-carotene supplements in tobacco smokers are a cause of lung cancer and that selenium probably protects against prostate cancer, while there was limited evidence indicating that vitamin A, vitamin E, and selenium protect against squamous cell carcinoma of the skin, prostate cancer, and either lung cancer or colorectal cancer, respectively [10].

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▪ **2010년, 명승권 등, 종양학연보(Ann Oncol)**
22년간 발표된 **총 22편의 임상시험(총 16만 여명 대상)의 결과를 종합 '메타분석'**한 결과,

1) 비타민 A, E, 베타카로틴, 셀레늄과 같은 비타민/항산화 보충제를 복용하나 하지 않으나 **암 예방효과 없음.**
← 상대위험도, 0.99 (95% 신뢰구간: 0.96-1.03)

2) 방광암의 발생은 섭취하는 경우 그렇지 않은 경우보다 오히려 52% 높음.
← 상대위험도, 1.52 (95% 신뢰구간: 1.06-2.17)

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비타민/항산화제와 심혈관질환(2013, BMJ)

BMJ

BMJ 2013;346:f10 doi: 10.1136/bmj.f10 (Published 18 January 2013)

RESEARCH

Efficacy of vitamin and antioxidant supplements in prevention of cardiovascular disease: systematic review and meta-analysis of randomised controlled trials

OPEN ACCESS

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Abstract
Objective To assess the efficacy of vitamin and antioxidant supplements in the prevention of cardiovascular diseases.
Design Meta-analysis of randomised controlled trials.
Data sources and study selection PubMed, EMBASE, the Cochrane Library, Scopus, CINAHL, and ClinicalTrials.gov searched in June and November 2012. Two authors independently reviewed and selected eligible randomised controlled trials, based on predetermined selection criteria.
Results Out of 2240 articles retrieved from databases and relevant bibliographies, 50 randomised controlled trials with 294 478 participants (156 683 in intervention groups and 137 815 in control groups) were included in the final analyses. In a fixed effect meta-analysis of the 50 trials, supplementation with vitamins and antioxidants was not associated with reductions in the risk of major cardiovascular events (relative risk 1.00, 95% confidence interval 0.98 to 1.02; I^2=42%). Overall, there was no beneficial effect of these supplements in the subgroup meta-analyses by type of prevention, type of vitamins and antioxidants, type of cardiovascular outcomes, study design, methodological quality, duration of treatment, funding source, provider of supplements, type of control, number of participants in each trial, and supplements given singly or in combination with other supplements. Among the subgroup meta-analyses by type of cardiovascular outcomes, vitamin and antioxidant supplementation was associated with a marginally increased risk of angina pectoris, while low dose vitamin B_6 supplementation was associated with a slightly decreased risk of major cardiovascular events. Those beneficial or harmful effects disappeared in subgroup meta-analysis of high quality randomised controlled trials within each category. Also, even though supplementation with vitamin B_6 was associated with a decreased risk of cardiovascular death in high quality trials, and vitamin E supplementation with a decreased risk of myocardial infarction, those beneficial effects were seen only in randomised controlled trials in which the supplements were supplied by the pharmaceutical industry.
Conclusion There is no evidence to support the use of vitamin and antioxidant supplements for prevention of cardiovascular diseases.

Introduction

Cardiovascular diseases are the leading causes of deaths and disability worldwide.[1] Over the past few decades, observational epidemiological studies have reported that intake of fruit and vegetables rich in various vitamins and antioxidants reduce the risk.[2] It has been estimated that if an individual increases fruit and vegetable intake up to 600 g daily, the worldwide burden of disease could be reduced by 31% for ischaemic heart disease and 19% for ischaemic stroke.[3] Unlike the evidence for fruit and vegetables, however, many randomised controlled trials have reported inconsistent findings regarding the efficacy of

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▪ **2013년 1월, 명승권 등**
23년간 발표된 **총 50편의 임상시험(총 29만 여명 대상)의 결과를 종합 '메타분석'**한 결과,

비타민/항산화 보충제를 복용하나 하지 않으나 **심혈관질환 예방효과 없음.**

← 상대위험도, 1.00
(95% 신뢰구간: 0.98-1.02)

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미국 질병예방서비스특별위원회(2014년 2월 최신권고안)

U.S. Preventive Services Task Force

Vitamin, Mineral, and Multivitamin Supplements for the Primary Prevention of Cardiovascular Disease and Cancer: U.S. Preventive Services Task Force Recommendation Statement
DRAFT

Summary of Recommendations and Evidence

The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of the use of multivitamins for the prevention of cardiovascular disease or cancer.

This is an I statement.

The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of the use of single- or paired-nutrient supplements (with the exception of beta-carotene and vitamin E) for the prevention of cardiovascular disease or cancer.

This is an I statement.

The USPSTF recommends against the use of beta-carotene or vitamin E supplements for the prevention of cardiovascular disease or cancer.

This is a D recommendation.

- 암이나 심혈관질환의 예방을 위해 종합비타민 등을 권고하거나 권고를 반대할 근거가 불충분함.
- 암이나 심혈관질환의 예방을 위해 베타카로틴이나 비타민E는 사용해서는 안됨.

오메가-3 지방산 보충제와 심혈관질환

오메가-3 지방산

▪ 1970년대 보고

- 그린란드에 사는 에스키모인들은 심혈관질환 발생이 적음.
- 이유: 오메가-3 지방산이 풍부한 등푸른생선이나 바다표범 섭취.

국제암대학원대학교 Graduate School of Cancer Science and Policy

국립암센터 NATIONAL CANCER CENTER

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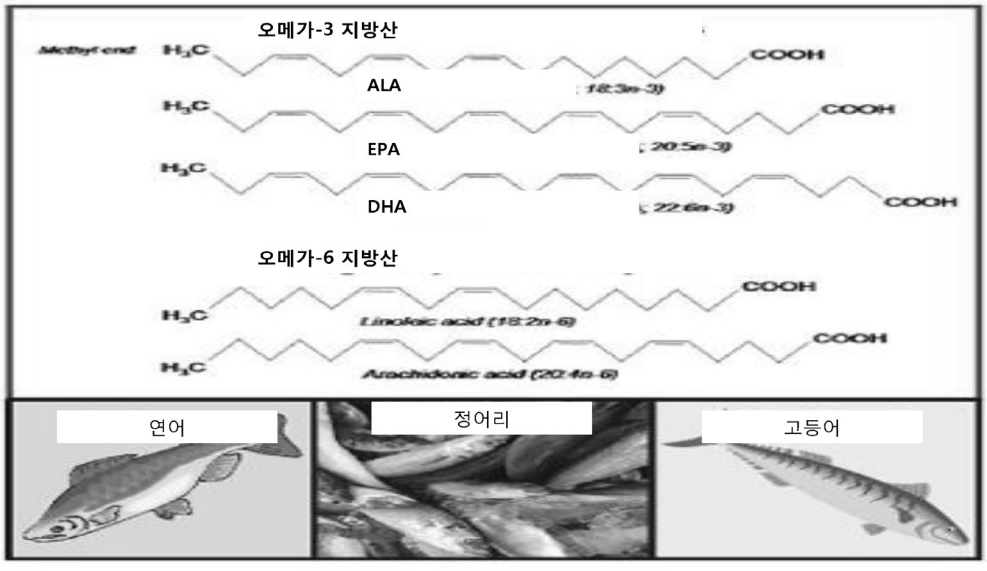
오메가-3 지방산이란?

▪ 지방을 구성하는 필수지방산으로 **항부정맥, 항죽상혈전, 지질감소, 혈관확장을 통해 심혈관질환예방 가능할 것으로 추정**



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오메가-3 지방산의 심혈관질환 예방 근거

- 1970년대 이후 많은 관찰연구(환자-대조군연구 및 코호트연구)
  - 생선이나 생선기름 섭취를 많이 한 사람들은 심혈관질환이 적음.

- 대규모 임상시험
  - 1만 천여명 심근경색환자(이탈리아, 1999년)와 1만8천여명 고지혈증 환자(일본, 2007년)를 대상.
  - 오메가-3 지방산 보충제 복용군이 복용하지 않은 군보다 심혈관질환이 적었음을 보고. (위약을 사용하지 않은 단점)

- 이후 최근까지 효과가 없다는 임상시험이 계속 발표됨.
- 현재 건강기능식품 생리활성기능 2등급.

REVIEW ARTICLE

ONLINE FIRST

Efficacy of Omega-3 Fatty Acid Supplements (Eicosapentaenoic Acid and Docosahexaenoic Acid) in the Secondary Prevention of Cardiovascular Disease

A Meta-analysis of Randomized, Double-blind, Placebo-Controlled Trials

Sang Mi Kwak, MD; Seung-Kwon Myung, MD; Young Jae Lee, MD, MS; Hong Gwan Seo, MD, PhD; for the Korean Meta-analysis Study Group

Background: Although previous randomized, double-blind, placebo-controlled trials reported the efficacy of omega-3 fatty acid supplements in the secondary prevention of cardiovascular disease (CVD), the evidence remains inconclusive. Using a meta-analysis, we investigated the efficacy of eicosapentaenoic acid and docosahexaenoic acid in the secondary prevention of CVD.

Methods: We searched PubMed, EMBASE, and the Cochrane Library in April 2011. Two of us independently reviewed and selected eligible randomized controlled trials.

Results: Of 1007 articles retrieved, 14 randomized, double-blind, placebo-controlled trials (involving 20 485 patients with a history of CVD) were included in the final analyses. Supplementation with omega-3 fatty acids did not reduce the risk of overall cardiovascular events (relative risk, 0.99; 95% CI, 0.89-1.09), all-cause mortality, sudden cardiac death, myocardial infarction, congestive heart failure, or transient ischemic attack and stroke. There was a small reduction in cardiovascular death (relative risk, 0.91; 95% CI, 0.84-0.99), which disappeared when we excluded a study with major methodological problems. Furthermore, no significant preventive effect was observed in subgroup analyses by the following: country location, inland or coastal geographic area, history of CVD, concomitant medication use, type of placebo material in the trial, methodological quality of the trial, duration of treatment, dosage of eicosapentaenoic acid or docosahexaenoic acid, or use of fish oil supplementation only as treatment.

Conclusion: Our meta-analysis showed insufficient evidence of a secondary preventive effect of omega-3 fatty acid supplements against overall cardiovascular events among patients with a history of cardiovascular disease.

Arch Intern Med.
Published online April 9, 2012.
doi:10.1001/archinternmed.2012.262

Author Affiliations: Center for Cancer Prevention and Detection (Drs Kwak, Myung, and Seo) and Cancer Epidemiology Branch, Research Institute (Dr Myung), National Cancer Center, Ilsan, Department of Family Medicine, School of Medicine, Seoul National University, Seoul (Dr Myung), and Anesthesiology and Pain Medicine, Armed Forces Capital Hospital, Seongnam (Dr Lee), Republic of Korea.
Group Information: The Korean Meta-analysis Study Group members are listed on page E8.

IN THE 1970s, BANG ET AL,[1] BANG and Dyerberg,[2] and Dyerberg et al[3] suggested that consumption of a large amount of fish or marine mammals rich in omega-3 fatty acids contributes to a low incidence of cardiovascular disease (CVD) among the Greenland Eskimos. Based on results of animal investigations, epidemiological studies, and randomized trials, numerous researchers reported cardiovascular effects of 2 major long-chain omega-3 polyunsaturated fatty acids, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). The evidence from those studies[4-8] indicates that omega-3 fatty acids have anti-inflammatory, antiatherogenic, and antiarrhythmic effects, which are considered plausible mechanisms for reducing the risk of CVD.

See Invited Commentary at end of article

Previous investigators reported inconsistent findings in animal studies of atherosclerosis. Some studies[9-11] found that fish oil reduced atherogenesis, while other researchers reported no effect[12,13] or negative effects.[14,15] The authors of a systematic review[16] and a meta-analysis[17] of observational investigations among case-control studies and cohort studies reported that fish or fish oil consumption has a protective effect against CVD.

- **2012년 4월 9일, 명승권 등, Arch Intern Med**

- 14편의 위약을 사용한 임상시험을 종합 메타분석

- 오메가-3 지방산 보충제는 심혈관질환 과거력이 있는 사람에서 2차적인 **심혈관질환 예방에 효과가 없었음.**
  (RR 0.99, 95%CI = 0.89-1.09)

국외 및 국내 언론보도

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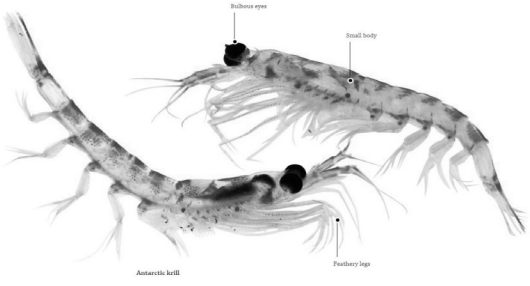
크릴오일과 이상지질혈증



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크릴오일 열풍!

홍보되고 있는 크릴오일의 효능

***주요 성분: 인지질, 오메가3, 아스타잔틴**

- **인지질**
  - 세포막의 주성분으로 혈전과 콜레스테롤을 제거함

- **오메가3**
  - 인지질에 부착되어 흡수되기 때문에 체내 흡수율이 높음. 중성지방 떨어뜨리고 인지기능 높아 치매 예방에도 도움.

- **아스타잔틴**
  - 강력한 항산화제로 암, 심혈관질환 및 각종 질병 예방

근거중심의학에 기반한 크릴오일의 잠재적 효능과 제한점

- 크릴오일 효능의 핵심은 오메가3 지방산이 풍부하며 기존 생선오일보다 흡수가 잘 된다는 것.
- 오메가3 지방산은 실험실 연구 및 동물실험을 통해 혈관확장, 항죽상혈전, 항부정맥, 중성지방 등 혈중 지질수치 개선을 통해 심혈관질환의 예방이 가능할 것으로 제기됨.
- 적지 않은 임상시험에서 오메가 3 지방산 보충제 복용은 중성지방 수치를 떨어뜨리는 것으로 나옴. **그러나!**

근거중심의학에 기반한 크릴오일의 잠재적 효능과 제한점

RESEARCH ARTICLE

Omega-3 Fatty Acid Supplements

European Journal of Lipid Science and Technology
www.ejlst.com

Use of Omega-3 Fatty Acid Supplements Has Insufficient Clinical Evidence for Treatment of Hypertriglyceridemia: A Meta-Analysis of Randomized, Double-Blind, Placebo-Controlled Trials

Gina E. Nam, Seung-Kwon Myung, and Yoon-Jung Choi*

Omega-3 fatty acid supplements have been used to treat dyslipidemia. However, there is no comprehensive meta-analysis of randomized, double-blind, placebo-controlled trials that encompasses a broad range of populations with or without underlying diseases regarding their efficacy. PubMed, EMBASE, and Cochrane Library were searched for trials in June 2016. A pooled weighted mean difference with its 95% confidence interval (CI) was calculated using a random-effect meta-analysis. A total of 58 trials were included in the final analysis. Compared with placebo, omega-3 fatty acid supplements significantly reduced triglyceride (TG) levels by 38.59 mg dL^{-1} (95% CI, −47.16 to −30.02 mg dL^{-1}; $n = 53$). In the subgroup meta-analysis, the beneficial effects on TG levels were dose-dependent up to 3.9 g of omega-3 fatty acid supplements daily and were greater at higher baseline TG levels. However, there existed substantial heterogeneity in the main and subgroup meta-analyses, overall methodological quality of included trials were low, and about 70% of the included trials had a small sample size less than 100 participants. The current meta-analysis of randomized, double-blind, placebo-controlled trials suggests that there is no sufficient clinical evidence to support the use of omega-3 fatty acid supplements for the prevention or treatment of dyslipidemia.

Practical Applications: **Further large, high-quality randomized, double-blind, placebo-controlled trials with a long-term follow-up are warranted to confirm the clinical efficacy of omega-3 fatty acid supplements on lipid profiles management.**

1. Introduction

Abnormal lipid serum levels (i.e., triglycerides [TG], total cholesterol, high-density lipoprotein cholesterol [HDL-C], and low-density lipoprotein cholesterol [LDL-C]) are identified as risk factors for various cardiovascular diseases.[1] According to the Global Health Observatory data repository of the World Health Organization (WHO), Europe has the highest prevalence (53.7%) of high cholesterol (≥5.5 mmol L^{-1} = 193 mg dL^{-1}) in the world, while its global prevalence is 38.9%.[2] Also, nearly 5.9% of adults aged 20 years or over are reported to have abnormal lipid profiles in the United States, and about 25–35% had hypertriglyceridemia.[3]

In patients with moderately elevated TG levels (150–500 mg dL^{-1}), the current National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) guidelines recommend lowering LDL-C levels as the primary therapeutic goal.[4] However, lowering TG levels become the focus in patients with severe hypertriglyceridemia (TG levels ≥ 500 mg dL^{-1}), which increases the risk of acute pancreatitis.[5] Pharmacological interventions include statins, fibrate, niacin, or omega-3 fatty acids to lower the elevated TG levels, in addition to therapeutic lifestyle changes.[6] Among treatment options, long chain omega-3 fatty acids such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are available as both prescription formulations and dietary supplements.

Potential mechanisms of the TG-lowering action by omega-3 fatty acids include reducing TG synthesis/secretion and enhancing TG clearance from very low-density lipoprotein cholesterol (VLDL-C).[7] It has been reported that daily intakes of 4 g of omega-3 fatty acid supplements help

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- 2017년 12월 유럽지질과학기술저널 (European Journal of Lipid Science and Technology)
- **<u>오메가3 지방산 보충제는 고중성지방혈증의 치료에 임상적 근거가 불충분하다!</u>**
- 58편의 임상시험 메타분석
- 책임저자: 명승권

근거중심의학에 기반한 크릴오일의 잠재적 효능과 제한점

Special Article

Lipid-modifying effects of krill oil in humans: systematic review and meta-analysis of randomized controlled trials

Sorin Ursoniu, Amirhossein Sahebkar, Maria-Corina Serban, Diana Antal, Dimitri P. Mikhailidis, Arrigo Cicero, Vasilios Athyros, Manfredi Rizzo, Jacek Rysz, Maciej Banach; for the Lipid and Blood Pressure Meta-analysis Collaboration Group

Context: *Some experimental and clinical trials have shown that krill oil, extracted from small red crustaceans, might be an effective lipid-modifying agent, but the evidence is not conclusive.* **Objective:** *The effect of krill oil supplements on plasma lipid concentrations was assessed through a systematic review of the literature and a meta-analysis of available randomized controlled trials.* **Data sources:** *PubMed and Scopus were searched up to March 25, 2016, to identify RCTs investigating the effect of krill oil supplements on plasma lipids.* **Study selection:** *Randomized controlled trials that investigated the impact of at least 2 weeks of supplementation with krill oil on plasma/serum concentrations of at least one of the main lipid parameters (ie, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, or triglycerides) and that reported sufficient information on plasma/serum lipid levels at baseline and at the end of study in both krill oil and control groups were eligible for inclusion.* **Data extraction:** *Two reviewers independently extracted the following data: first author's name, year of publication, study location, study design, number of participants in the krill oil and control groups, dosage of krill oil, type of control administration, treatment duration, demographic characteristics of study participants, and baseline and follow-up plasma concentrations of lipids. Effect size was expressed as the weighted mean difference (WMD) and 95% confidence interval (95%CI).* **Results:** *Meta-analysis of data from 7 eligible trials (14 treatment arms) with 662 participants showed a significant reduction in plasma concentrations of low-density lipoprotein cholesterol (WMD, −15.52 mg/dL; 95%CI, −28.43 to −2.61; P = 0.018) and triglycerides (WMD, −14.03 mg/dL; 95%CI, −21.38 to −6.67; P < 0.001) following supplementation with krill oil. A significant elevation in plasma concentrations of high-density lipoprotein cholesterol was also observed (WMD, 6.65 mg/dL; 95%CI, 2.30 to 10.99; P = 0.003), while a reduction in plasma concentrations of total cholesterol did not*

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Key words: Euphausiacea krill, krill oil, meta-analysis, plasma lipids.

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- 2017년 15월 영양리뷰(Nutrition Reviews)
- 7편의 임상시험 메타분석
- **크릴오일 복용군에서 LDL(저밀도 콜레스테롤) 15mg/dL, TG (중성지방) 14mg/dL 감소.**
- 제한점: 662명으로 소수, 중성지방감소는 12주이상 복용시에만 관찰. 심혈관질환의 위험성에 대해서는 추가적인 연구 필요.

근거중심의학에 기반한 크릴오일의 효능에 대한 결론

- 크릴오일은 생선오일과 비교 시 흡수가 잘 되고 복용이 편하다는 장점
- 하지만, 현재까지 7편의 소수의 임상시험을 종합한 메타분석에서 중성지방과 저밀도 콜레스테롤 수치를 감소시킨다는 결과가 나왔지만,
- 중성지방의 경우 12주 이상 복용 시에만 감소효과 관찰되었고, 662명의 소수의 연구대상자며
- 지질감소가 결국 협심증, 심근경색증, 뇌경색 등 심혈관질환 예방에 도움이 되는지는 더 많은 임상시험이 필요하며
- 중성지방이 높은 경우 원인이 되는 음주, 비만, 음식 조절을 며칠 혹은 1주만 시행해도 낮아질 수 있어 생활습관개선이 중요함.

오메가-3 지방산 섭취 어떻게 해야하나?

▪ 오메가-3 지방산 보충제는 심혈관질환 과거력이 있는 사람에게 도움이 되지 않음.

▪ 건강인의 경우에는 임상시험 자체가 없기 때문에 더욱 권장할 수 없음.

▪ 오메가-3 지방산이 풍부한 등푸른생선을 1주일에 2회 정도(1회 100g, 손바닥 크기) 섭취할 것을 권장.

2017년 상반기 등급제 폐지

헤럴드경제 코리아헤럴드 슈퍼리치 헤럴드POP K-POP헤럴드 주니어헤럴드

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식약처, 건강기능식품 기능성 인정 까다롭게 한다

2015.08.20.

[헤럴드경제=김성훈 기자] 정부가 건강기능식품에 대해 상시적으로 재평가하고, 인체에 해가 되는 원료를 사용할 경우 처벌하겠다는 방침을 밝혔다. '가짜 백수오 사건' 당시 지적이 일었던 일련의 문제들에 대한 대책이다.

식품의약품안전처는 건강기능식품의 기능성을 5년에 한 번 씩 다시 평가하도록 하는 방안을 추진하기로 했다고 20일 밝혔다. 그동안 건강기능식품은 한번 기능성을 인정받으면 기능성이 그대로 유지되는지를 재평가받지 않았지만, 백수오의 기능성에 의문을 제기하는 목소리가 이어지자 이같은 방안을 내놓은 것이다. 더불어 5명 이상의 소비자가 피해를 신고하는 등 필요할 때에는 즉각적으로 재평가하는 방안도 추진할 방침이다.

식약처는 또 인체에 독성이 있거나 부작용을 일으키는 원료에 대한 사용금지 규정을 만들어 위반하면 10년 이하의 징역과 1억원 이하의 벌금을 부과하는 등 강도 높게 처벌할 계획이다. 위해 발생 우려가 있을 때에는 위해 여부가 확인되기 전에도 해당 건강기능식품의 제조와 판매를 금지하는 긴급 대응 조치 제도를 도입하기로 했다.

건강기능식품의 기능성 인정 체계도 개편된다. 식약처는 그간 건강기능식품의 원료를 기능성이 높은 순서대로 4단계로 나눠 질병발생위험감소기능(질병의 발생 위험 감소에 도움을 주는 경우), 생리활성기능 1등급(특정 기능에 도움을 줌), 2등급(특정 기능에 도움을 줄 수 있음), 3등급(특정 기능에 도움을 줄 수 있으나 관련 인체적용시험이 미흡함) 중 하나를 부여해왔다. 그러나 앞으로는 질병발생위험감소기능과 생리활성기능 1등급, 2등급을 통합하는 대신 상대적으로 쉽게 건강기능식품 원료로 인정받을 수 있었던 생리활성기능 3등급을 없앨 방침이다. 기능성 인정 체계를 1단계로 통합하고 기능성 인정 조건도 까다롭게 하는 것이다.

식약처는 또 건강기능식품 원재료의 진위 확인 의무를 제조업체에 부과하기로 했다. 육안으로 구별이 어려운 원재료는 시험·검사해 그 결과를 기록하는 방식으로 관리하도록 의무화하기로 했다. 2017년까지 건강기능식품 제조·수입·판매업소 이력추적관리 제도를 단계적으로 확대해 원재료 관리를 강화할 계획이다.

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요약

▪ 파이토뉴트리언트(파이토케미칼)는 실험실 연구, 동물연구 등 전임상연구와 역학관찰연구를 종합한 메타분석 등에서 음식을 통한 섭취는 이상지질혈증이나 심혈관질환의 위험성을 감소시키는 긍정적인 효과가 관찰됨.

▪ 하지만, 음식이 아닌 파이토뉴트리언트 보충제의 복용은 일부 무작위 비교 임상시험(RCT)을 통해 고용량의 복용 시 이상지질혈증에 긍정적인 효과가 보고되고 있지만, 궁극적으로 심혈관질환의 예방에 도움이 되는지에 대한 임상시험은 부족해 그 근거가 없음.

▪ 비타민 및 항산화제, 칼슘, 오메가3 지방산/크릴오일 등의 건강기능식품 역시 심혈관질환의 예방이나 치료에 임상적 근거가 부족함.