THERAPEUTICS

Review: High-dose vitamin E supplementation is associated with increased all-cause mortality

Miller ER III, Pastor-Barriuso R, Dalal D, et al. **Meta-analysis: high-dosage vitamin E supplementation may increase all-cause mortality.** Ann Intern Med. 2005;142:37-46.

Clinical impact ratings: GIM/FP/GP ★★★★★☆☆ Cardiology ★★★★★★☆

QUESTIONS

Does vitamin E supplementation increase all-cause mortality? Does a dose-response relation exist between vitamin E and all-cause mortality?

METHODS

Data sources: MEDLINE (1966 to August 2004), Cochrane Central Register of Controlled Trials, bibliographies of relevant studies and reviews, and personal files of the investigators.

Study selection and assessment: Randomized controlled trials (RCTs) that compared vitamin E supplementation (alone or combined with other vitamins or minerals) with a control or placebo group in men or nonpregnant women, study duration and follow-up was > 1 year, and ≥ 10 deaths occurred.

Outcomes: All-cause mortality.

MAIN RESULTS

19 RCTs (n = 135 967, mean age range 47 to 84 y) met the selection criteria. 9 RCTs used vitamin E alone, and 10 combined vitamin E with other vitamins or minerals. 16 RCTs were placebo-controlled. Vitamin E dose varied between 16.5 and 2000 IU/d. Overall, vitamin E supplementation did not affect all-cause mortality (Table). Results differed between low-dose (< 400 IU/d) and high-dose (≥ 400 IU/d) trials: Mortality was not increased in 8 RCTs evaluating low-dose vitamin E, while high-dose vitamin E was associated with increased mortality (11 RCTs) (Table). A dose-response analysis showed all-cause mortality increased as vitamin E dose increased > 150 IU/d. The effect of vitamin E did not change after adjustment for differences in sex, mean age, or mean follow-up. The association of high-dose vitamin E and mortality was stronger after adjustment for concomitant use of other vitamins and minerals (pooled relative risk 1.06, 95% CI 1.01 to 1.11; risk difference 63 per 10 000 persons, CI 6 to 119).

CONCLUSIONS

High-dose (≥ 400 IU/d) vitamin E supplementation is associated with increased risk for all-cause mortality. A dose-response relation exists between mortality and vitamin E doses > 150 IU/d.

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High (≥ 400 IU/d), low (< 400 IU/d), and all doses of vitamin E supplementation vs placebo or no vitamin E for all-cause mortality*

Number of trials (n)	Vitamin E dose	RRI (95% CI)	Risk difference per 10 000 persons (CI)	NNH (CI)
19 (135 967)	High and low	1% (–2 to 4)	10 (–18 to 38)	Not significant
11 (40 950)	High	4% (1 to 7)	39 (3 to 74)†	257 (136 to 3334)
		RRR (CI)		NNT
8 (95 017)	Low	2% (–1 to 4)	–16 (–41 to 10)	Not significant

*Abbreviations defined in Glossary; RRI, RRR, NNH, NNT, and CI calculated from data in article. Follow-up ranged from 1.4 to 8.2 years. A dose-response regression model was used.
†Favors placebo or no vitamin E.

COMMENTARY

On June 8, 1946, a letter was published in *Nature* on the benefits of vitamin E for heart disease (1). In response to extensive press coverage, an editorial appeared in *JAMA* later that month cautioning, "The reported discovery of new and almost miraculous powers of vitamin E needs careful evaluation and confirmation…" (2). Initially it was theorized that the beneficial effects of vitamin E on the heart might derive from its antithrombin or vasodilatory properties. The modern observation that oxidatively modified, low-density lipoprotein cholesterol promotes atherosclerosis led to renewed interest in vitamin E as an antioxidant.

The review by Miller and colleagues is the fifth meta-analysis or comprehensive review of the clinical trial evidence on vitamin E in the recent past (3–6). These reviews have differed somewhat (e.g., only analyzing trials enrolling ≥ 1000 patients [3] or evaluating primary coronary heart disease [CHD] prevention studies separately from secondary CHD prevention studies [4]), but have reached a similar conclusion: Vitamin E supplementation does not decrease the risk for CHD events.

Unlike the other reviews, Miller and colleagues chose to divide the clinical trials by the dose of vitamin E administered, comparing low-dose studies (< 400 IU/d) with high-dose studies (≥ 400 IU/d). When analyzed in this fashion, vitamin E ≥ 400 IU/d was associated with a 4% relative risk increase in death (about a 0.4% absolute risk increase). Low-dose vitamin E was associated with no increased risk or possibly even a slightly decreased risk for death. Because the meta-analysis pooled studies of persons with or at risk for chronic disease, it is unknown whether the results apply to healthy persons.

While antioxidants remain an important area for research, physicians should focus on proven CHD risk-factor reduction. For at-risk patients who are determined to use vitamin E, keeping the dose below 150 IU/d would be prudent.

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