

Folate plus vitamin B₁₂ reduced hip fractures in patients with poststroke hemiplegia

Sato Y, Honda Y, Iwamoto J, Kanoko T, Satoh K. Effect of folate and mecobalamin on hip fractures in patients with stroke: a randomized controlled trial. *JAMA*. 2005;293:1082-8.

Clinical impact ratings: GIM/FP/GP ★★★★★☆ Geriatrics ★★★★★☆ Neurology ★★★★★☆

QUESTION

Does treatment with folate and vitamin B₁₂ reduce hip fractures in patients with hemiplegia after ischemic stroke?

METHODS

Design: Randomized placebo-controlled trial.

Allocation: Concealed.*

Blinding: Blinded {patients, health care providers, data collectors, data analysts, monitoring committee, and manuscript writers}†.*

Follow-up period: 2 years.

Setting: A hospital in Iizuka, Japan.

Patients: 628 patients ≥ 65 years of age (mean age 71 y, 54% women) who had a first-ever noncardioembolic ischemic stroke more than 1 year before and were in a convalescent stage with poststroke hemiplegia. Exclusion criteria were history of fracture; impaired hepatic, renal, cardiac, or thyroid function; known causes of osteoporosis; or use of drugs known to alter bone and methionine metabolism (e.g., corticosteroids, anticonvulsants, estrogens, calcitonin, bisphosphonates, calcium folate, or vitamins B₆, B₁₂, D, or K) for ≥ 3 months in the previous year.

Intervention: 314 patients were allocated to daily folate (Foliamin, Nihon Pharmaceuticals, Tokyo, Japan), 5 mg, and mecobalamin (Methycobal, Eisai Pharmaceuticals, Tokyo, Japan), 1500 µg, and 314 were allocated to double placebo.

Outcome: Incidence of hip fracture.

Patient follow-up: 89% completed the trial. All patients were included in the intention-to-treat analysis.

MAIN RESULTS

At 2 years, patients in the treatment group had a lower risk for hip fracture or any fracture than did those in the placebo group (Table). The numbers of hip fractures per 1000 patient-years in the treatment and placebo groups were 1.9 and 8.6, respectively. Over the 2-year period, the groups did not

differ for the number of falls per patient (2.3 vs 2.2) or mean percentage change in bone mineral density in the hemiplegic side (-2.9 vs -3.0, *I*₂ = 0.69) or the intact side (-1.9 vs -1.9, *P* = 0.12).

CONCLUSION

Combined folate and vitamin B₁₂ therapy reduced the risk for hip fracture at 2 years in patients with poststroke hemiplegia.

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*See Glossary.

†Information provided by author.

Folate plus vitamin B₁₂ (mecobalamin) vs double placebo for patients with poststroke hemiplegia†

Outcomes at 2 y	Folate plus vitamin B ₁₂	Placebo	RRR (95% CI) [§]	NNT (CI) [§]
Hip fractures	1.9%	8.6%	80% (50 to 92)	14 (9 to 28)
All fractures	2.5%	10%	76% (47 to 89)	13 (9 to 25)

‡Abbreviations defined in Glossary. Event rates calculated from data in article.

§Adjusted for dementia, cardiovascular events, and subsequent stroke.

COMMENTARY

Stroke dramatically increases the risk for hip and other fractures (1). Elevated homocysteine levels indicate a ≥ 2-fold increased risk for hip fracture (2,3) that is not caused by decreased bone mass (2). Folate with vitamin B₁₂ lowers homocysteine levels, and Sato and colleagues report that folate and vitamin B₁₂ supplementation decreased the risk for fracture by about 80% without improving bone mass or reducing risk for falling. The huge reduction in risk defies explanation by current paradigms of pathogenesis and prevention of fractures. Homocysteine might weaken bone by binding to cross-links in collagen; however, bone collagen has a half-life > 10 years, which precludes such a dramatic change in collagen strength during a 2-year trial. The description of the trial reveals no flaw that could account for this result.

The generalizability of the results is limited for such countries as the United States, which have begun to fortify foods with folate. Thus, confirmation of these astonishing results may not be possible in these countries.

Meanwhile, it is reasonable to give these inexpensive and safe vitamins to patients with stroke. However, we should not rely on this strat-

egy to substantially reduce fracture risk after stroke. Patients who have had a stroke often have vitamin D deficiency and should receive at least 800 IU daily. In a very small trial, Sato and colleagues also reported that risenedronate reduced the risk for hip fracture in women after stroke (4). More convincing results from large trials could make effective prevention of fractures part of stroke-care protocols.

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References

- Kanis J, Oden A, Johnell O. Acute and long-term increase in fracture risk after hospitalization for stroke. *Stroke*. 2001;32:702-6.
- van Meurs JB, Dhonukshe-Rutten RA, Pluijm SM, et al. Homocysteine levels and the risk of osteoporotic fracture. *N Engl J Med*. 2004;350:2033-41.
- McLean RR, Jacques PF, Selhub J, et al. Homocysteine as a predictive factor for hip fracture in older persons. *N Engl J Med*. 2004;350:2042-9.
- Sato Y, Iwamoto J, Kanoko T, Satoh K. Risenedronate therapy for prevention of hip fracture after stroke in elderly women. *Neurology*. 2005;64:811-6.