sex hormone–binding globulin (SHBG) (8). Elevated insulin, IGF-1, sex hormones, or decreased concentrations of SHBG (or all 4) have been associated with a greater risk of a range of cancers, including premenopausal breast (9) and colorectal (10, 10) cancer.

Therefore, dietary patterns that stimulate postprandial elevations in blood glucose and insulin concentrations, such as those with a high GI and GL, may potentially increase the risk of a range of diseases, including type 2 diabetes, cardiovascular disease, and some cancers.

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REFERENCES


Folic acid supplements are good (not bad) for rheumatoid arthritis patients treated with low-dose methotrexate

Dear Sir:

The interesting and provocative commentary on folic acid fortification and supplementation by Smith et al (1) seems to contain a conceptual error in the “thought experiment” involving folic acid supplements and the use of methotrexate (MTX) in the treatment of autoimmune disease such as rheumatoid arthritis (RA) and psoriasis. Folic acid supplements are routinely used to reduce the toxicity of low-dose MTX (usually to the gastrointestinal system, liver, and bone marrow) in the treatment of autoimmune disease such that the patient may experience the efficacy of this drug without its toxicity (ie, an increase in the therapeutic index) (2). A major reason for stopping low-dose MTX therapy is drug toxicity, not a lack of efficacy (3). Thus, it is unethical to continue to use MTX to treat RA patients who develop conditions such as stomatitis, elevated concentrations of liver function enzymes, and cytopenias, even though their joint disease is greatly reduced. In addition, many nonsteroidal anti-inflammatory drugs (NSAIDs) are used in high doses with MTX in RA therapy, and many NSAIDs also have antifibole activities (4). Medical emergencies have been reported in patients taking MTX in combination with other antifolates (5). Because of its remarkable efficacy, MTX is the “gold standard” drug for RA therapy and an anchor drug to which other drugs or biologicals are added (6, 7). Over the past few decades, rheumatologists have become more confident in the use of MTX, especially because its associated toxicity is manageable with folic acid supplements; therefore, it is more widely used at higher doses to achieve better responses. Confidence in the use of higher doses has likely occurred at the same time as folic acid fortification; therefore, higher doses cannot necessarily be attributed only to folate fortification (8).

The post hoc analysis of the 2 randomized trials that found that patients who were taking folic acid had a poor clinical response to MTX (9) has been criticized because of I( differences in the patient’s baseline characteristics, 2) the lack of a placebo group in the European Study, J) the post hoc data interpretation, 4) differences in mean disease duration between the patients in the European and American trials, 5) a larger proportion of patients receiving NSAIDs in the European study, and 6) the similarity in response rates in the European and American studies at 2 y. Therefore, we suggest caution in using this as a piece of confirmatory data (10).

There is no evidence that food folate fortification has resulted in an increase in the incidence or severity of RA in the United States; however, on the other hand, there is a large group of patients with RA who have better-controlled disease because folic acid supplements allow them to tolerate MTX therapy. Although we agree that folic acid supplements may have exposed the general population to certain risks, it is generally accepted that modest amounts of this vitamin are beneficial to patients chronically treated with low-dose MTX.

No conflicts of interest were reported.

Jennie C Brand-Miller

Alan W Barclay

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2. Morgan SL, Baggott JE, Vaughn WH, et al. Supplementation with folic...


Reply to E Baggott and SL Morgan

Dear Sir:

We agree with Baggott and Morgan that folic acid or its derivatives are valuable in reducing the toxic side effects of methotrexate in patients with rheumatoid arthritis (RA) and, indeed, we (1) pointed this out (page 523). However, we do not think we made a conceptual error in our “thought experiment”; what we wrote was that studies need to be done to determine whether the incidence or severity of RA and psoriasis have changed in countries that have introduced folic acid fortification. We also asked whether treatment choice or drug efficacy has changed in these countries. The report by Arabelovic et al (2) that appeared after our Commentary was submitted shows that the average dose of methotrexate used has increased in the United States since 1996; the explanation offered by Baggott and Morgan is just as speculative as the suggestion that this change is a consequence of fortification. A key question is whether Baggott and Morgan consider it ethical to give additional folic acid to untreated RA patients to see whether it changes their symptoms, even if such a trial were to take place in a country without fortification. We think not. Finally, to say that there is no evidence that fortification has increased the incidence of RA simply reflects the fact that no such study has been conducted. We believe that such studies should be conducted, in the same way as they have been to determine the incidence of cancer (3). What we need is more evidence.

No conflicts of interest were declared.

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REFERENCES


Erratum


In the third paragraph in the left-hand column on page 1229, the following sentence should have been deleted: “Linoleic acid...” In the same paragraph, the following sentence also should have been deleted: “Furthermore, as mentioned earlier, the body can convert linoleic acid into EPA and DHA (n–3 PUFAs).”