

Guest editorial

Folic acid, folate and homocysteine: human intervention studies

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Folate is the generic name for all derivatives of the B vitamin with the biological activity of pteroylmonoglutamic acid. Folic acid is the fully oxidised monoglutamate form of the vitamin, whereas the other naturally occurring forms are referred to as folates. Folic acid supplementation around conception decreases the risk of having offspring with a neural-tube defect [1,2]. Therefore, Governments in several countries advise women planning to become pregnant to consume additional folic acid or folate to prevent neural tube defects. Women who have not previously given birth to a child with a neural-tube defect are advised to take 400 to 500 μg additional folic acid or folate each day from at least 4 weeks before pregnancy until at least the eighth week of pregnancy. Although lower doses may be effective, no randomised trials have been carried out to test whether this is indeed the case. The underlying mechanism of the preventive effect of folic acid is unclear.

Some Governments specifically advise women to take additional synthetic folic acid, because the effectiveness of natural food folate might be lower. Folate in food occurs in many different forms. It is unclear whether high intakes of folate from food can also prevent neural-tube defects. Furthermore, it is difficult for women to reach a daily intake of 400 μg of dietary folate. The average intake is only about 250 μg per day [3]. On the other hand, not all women in the target group do take folic acid tablets around conception [4,5].

Women who previously gave birth to a child with a neural-tube defect were shown to have elevated plasma total homocysteine concentrations [6,7]. Thus, a decrease in homocysteine concentrations may result in a lower risk for having a child with a neural-tube defect. We showed in

a controlled dietary intervention study that a diet high in dietary folate from vegetables and citrus fruit (560 $\mu\text{g}/\text{d}$) decreased plasma total homocysteine concentrations and improved the folate status [8]. The bioefficacy of the dietary folate from vegetables and citrus fruit compared to folic acid was 60% in this study. The bioavailability was 78% when change in plasma folate was used as the determinant of bioavailability and 98% when change in red blood cell folate was used. However, women should still be advised to take additional folic acid to reduce the risk of having a child with a neural-tube defect. Firstly, the above-mentioned problems with the intake of dietary folate still exist. Secondly, lowering homocysteine may decrease the risk of having a child with a neural-tube defect, but it is not certain.

Most studies that have investigated the effect of folic acid supplementation on plasma total homocysteine concentration have focused on persons with plasma total homocysteine concentrations above the normal range. Refsum et al. concluded from a review of the literature that the relationship between plasma total homocysteine level and cardiovascular disease is continuous without an apparent threshold [9]. Therefore, the effect of intake of low doses of folic acid and of dietary folate on total plasma homocysteine concentrations in subjects with plasma total homocysteine concentrations in the normal range is of interest.

In a placebo-controlled study with 144 healthy women, we provided subjects with a normal homocysteine concentration, with either 500 μg of folic acid each day, 500 μg of folic acid every other day, or a placebo tablet daily for 4 weeks [10]. Both folic acid intervention strategies significantly improved plasma folate and red blood cell folate concentrations. Intervention with 500 μg of folic acid each day decreased plasma total homocysteine concentrations by 22% and intervention with 500 μg of folic

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acid every other day decreased the concentrations by 11%. Supplementation with 500 μg of folic acid each day caused the most distinct decrease in plasma total homocysteine concentrations in the first two weeks of supplementation. Plasma homocysteine and folate improved after as little as 1 week of supplementation. Neural tube closure takes place during the third and fourth week of supplementation. Therefore, our results suggest that the recommended period of folic acid use of 4 weeks before conception is sufficient to improve folate status. The results even suggest that if women did not take folic acid before pregnancy, for example in case of an unplanned pregnancy, it might still be worthwhile to start taking additional folic acid immediately after missing the first menstrual period.

To gain more knowledge of the aetiology behind the risk of having a neural tube defect, we performed a case-control study. We studied whether patients with spina bifida, a neural tube defect, have lower concentrations of blood folate and higher concentrations of fasting and post-methionine-load homocysteine concentrations. Moreover, effects of supplementation with 500 μg of folic acid daily on the folate and homocysteine status in spina bifida patients ($n=11$) and control patients ($n=12$) were determined. Although the small sample size of the study does not allow us from drawing firm conclusions, the study did not show a derangement in homocysteine metabolism in the spina bifida patients compared to the control patients. Folic acid supplementation seemed at least as effective in the spina bifida as in the control patients.

In conclusion, low-dose folic acid supplementation effectively improves folate status and decreases plasma homocysteine concentrations in healthy young women. Although a high intake of dietary folate from vegetables and citrus fruit also improves folate status and decreases plasma homocysteine concentrations, women planning to become pregnant should still be advised to take additional

synthetic folic acid. A high intake of dietary folate may decrease the risk of having a child with a neural tube defect, but intake of additional folic acid has been proven to do so.

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