BRIEF REPORT

Role of Folate in Management of Endothelial Dysfunction

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ABSTRACT

Folate is a vital nutrient with participation in one carbon reactions, purine synthesis, formation of methionine from homocysteine and DNA synthesis. Its deficiency has been linked with a spectrum of diseases like gastrointestinal disorders, glossitis, megaloblastic anemia, peripheral neuropathy and hyperhomocysteinemia. It is singularly eminent methyl donor in body for stability of the genome and orderly expression of genes. Over recent years, endothelial dysfunction is considered a key element of vascular pathology, including the coronary artery disease and hyperhomocysteinemia, is shown to worsen endothelial dysfunction. Folate deficiency is one etiological element for hyperhomocysteinemia and folate supplementation is tried with intent to reduce cardiovascular risk in patients. Inconsistency of beneficial outcomes, however, highlights complexities in occurrence of hyperhomocysteinemia , the determinants of endothelial dysfunction and consequent cardiovascular risk. Research has revealed new potentially beneficial action profiles of folic acid for improving endothelial dysfunction and cardiovascular risk independent of homocysteine reduction. Attempt is herein made to translate new knowledge to suit clinical exploitation. (J Clin Prev Cardiol 2013;2(2):91-4)

Keywords: Endothelial dysfunction, hyperhomocysteinemia, coronary disease risk, Folate, preventive nutrition.

Introduction

Endothelial dysfunction is considered as a hallmark in the pathogenesis of many cardiovascular disorders like myocardial infarction (MI), angina, stroke and diabetes (1, 2). It is a long-term predictor of the development of atherosclerosis and cardiovascular events and a useful surrogate marker for cardiovascular disease. A number of factors have been attributed to this including hyperlipidemia, hypertension, smoking, obesity and hyperhomocysteinemia (3). Elevated homocysteine levels affect endothelium by a number of ways such as generating excess of reactive oxygen species, causing peroxidation of lipids, impairing nitric oxide (NO) and direct endothelial toxicity (4). Homocysteine damages endothelium and decreases its ability to produce NO in response to stress and pharmacological stimuli by modifying eNOS activity (5). Further intracellular superoxides O_2 and peroxynitrites $ONOO^-$ have been found to increase with elevated homocysteine levels. Folate supplementation has been associated with reduced cardiovascular risk by decreasing homocysteine levels. Further, high single-dose and multiple-dose folic acid administration has been shown to prevent the temporary endothelial dysfunction induced by post-methionine-load hyperhomocysteinemia (6). But recent studies show a vasculoprotective action of folate independent of homocysteine diminution (7).

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Proposed Mechanisms of Folate in Cardiovascular Protection

A number of actions of folate are considered responsible for its endothelial protective role.

Reduction of Hyperhomocysteinemia

Since homocysteine is a definite contributor to cardiovascular risk (8), homocysteine conversion to methionine is supposed to be a key beneficial consequence of folate administration. Folate administration augments endothelial function assessed by ultrasound guided flow mediated dilation of brachial artery (9). Studies have shown significant reduction in homocysteine profiles in asymptomatic patients with hyperhomocysteinemia as well as in patients with coronary artery disease with elevated homocysteine which suggests homocysteine lowering by folate as an important mechanism (10,11). On the other hand in patients of homocysteinuria (serum homocysteine >300 µmol/L), with very high risk of developing coronary event, folate treatment led to remarkable reduction in oxidative stress and improvement in endothelial dysfunction without proportional reduction in levels of homocysteine (12). MTHF (Methyl tetrahydrofolate)

supplementation has also improved endothelial function in hypercholesterolemic patients without elevated levels of homocysteine (13). Even in those with significant coronary artery disease, endothelial protective action of folate was demonstrated independent of lowering of homocysteine levels (7). Vasculoprotective action of folate was found in one study to correlate better with reduction in free but not total homocysteine (14).

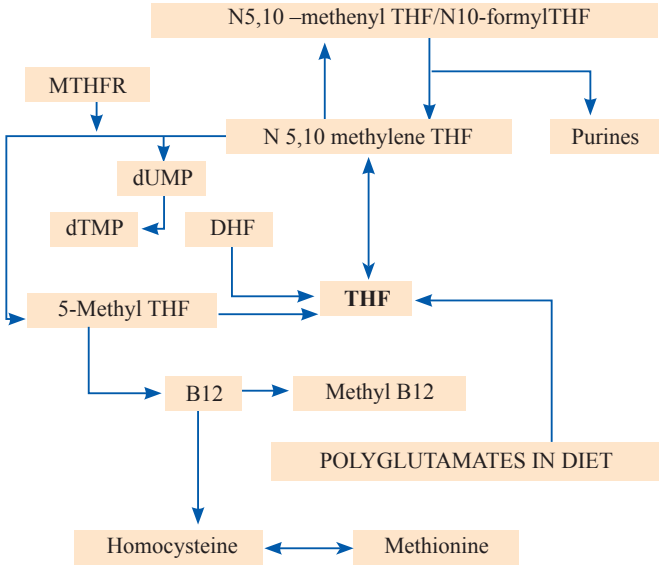

Figure 1. Folate Metabolism (the metabolic linkage of folate and homocysteine)[4]

Folate = Pteroylglutamic acid = Vitamin B9 is converted first into THF(Tetrahydrofolate) which then forms 5, 10 methylene THF .The latter is converted into methylTHF via MTHFR. Methyl THF after demethylation generates THF in the presence of Vitamin B12 and the methyl group thus released converts homocysteine into methionine. Thus absence of Vitamin B12 also leads to hyperhomocysteinemia via "Methyl trap" or Folate trap. Folate as shown in picture is also involved in purine and TMP synthesis.

Antioxidant action

Oxidative stress results from disequilibrium between the production of reactive oxygen species (ROS) and the tissue antioxidant defenses. Excess ROS formation is observed in conditions like diabetes, myocardial infarction, angina, congestive heart failure and Alzheimer's dementia (15). Reactive oxygen species interact with NO and form toxic peroxynitrite radicals with detrimental effects like oxidation of BH_4 (tetrahydrobiopterin) degradation of zinc-thiolate cluster involved in eNOS (nitric oxide synthase) coupling and degradation of GTP Cyclohydrolase (GTPCH1) enzyme involved in BH_4 synthesis. All these culminate in eNOS uncoupling so that NOS becomes a net producer of O_2^- and NO level in endothelium falls (16). Endothelial dysfunction is hence consequent to reduced bioavailability of endothelium-derived NO. MTHF has been shown to reduce the generation of oxidant species via its interaction with hypoxanthine/xanthine oxidase and eNOS (13). Folate deficiency in rats has been linked to high lipid peroxidation and reduced antioxidant defense mechanisms (17).

Interactions with eNOS

A pteridine binding site for folate has been demonstrated on eNOS as is on DHFR (dihydrofolatereductase) (18). eNOS enzyme is involved in NO synthesis in endothelium which is responsible for vasodilation in response to stress or pharmacological stimuli. It binds NADPH at the N terminal oxygenase site and O_2, BH_4 and arginine at the C terminal reductase site. BH_4 (tetrahydrobiopterin) is required for coupling of eNOS to NO synthesis. Folate has been shown to potentiate NO action and synthesis as depicted in Figure 2.

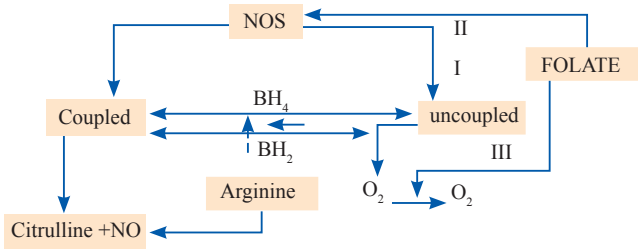

Figure 2. Folate has a number of roles to play with respect to NO synthesis. I. Stabilization of BH4 like Vitamin C (19) and its generation from BH2. II. Direct stimulant action NOS III. Antioxidant action of folate on oxidant species. Folate transfers electrons to heme moiety of NOS and activates O2.

It has been recently demonstrated that 5-methyl tetrahydrofolate 5 MTHF is the key regulator of eNOS coupling and NO availability in vessels and that homocysteine serves as an indirect regulator. Further folate supplementation in diabetic patients has been shown to improve insulin resistance (20). The endothelial protective effects of folate are seen at high doses and in early stages of atherogenesis (21). Only modest benefit is seen in the presence of advanced coronary artery disease and none in patients with end stage renal failure (22). Studies like Kuopio Ischaemic Heart Disease Risk Factor Study, the Framingham Heart Study, National health and Nutrition Examination Survey have displayed an inverse relationship between serum folate

and cardiovascular risk, although not supported by some groups (23). Nutrients, predominantly the vitamins, phytochemicals, types of fats and physical activity profiles have diverse molecular implications for the prevention and management of chronic inflammatory conditions (24).

Folic acid –B12 supplementation study in obese Type 2 diabetes patients (25)

A trial of assessing improvement in endothelial function by flow mediated dilatation of brachial artery after supplementation of folate at 5 mg and vitamin B12 at 500 µg in 32 obese patients with type 2 diabetes and BMI >25 kg/m^2 revealed uniform and highly significant improvement in endothelial function in folate group. No significant improvement was noticed in the control group (25).

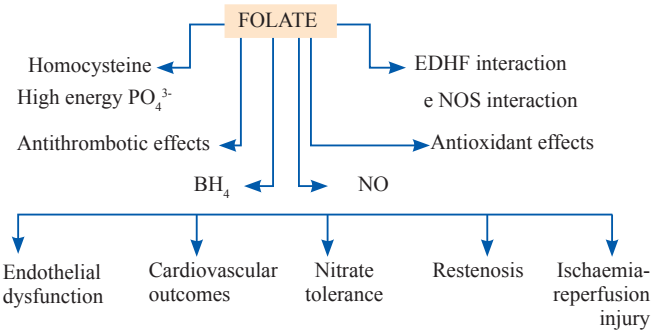

Figure 3. Showing various roles of folate.

Conclusion

Folate sufficiency was initially considered to be merely the absence of anemia. Reminiscence in folate biology has occurred since the demonstration of neural tube defects in infants born to folate deficient mothers. Now it is well supported that folate deficiency is associated with increased cardiovascular risk. Amount present in diet is not sufficient to prevent the risk of cardiovascular disease particularly when diet includes animal products which increase methionine in serum. The inconsistencies project strong imperatives for adequate translational efforts to define and diagnose appropriate indications, personalized contexts, optimal dose and synergetic nutrient regimens toward exploiting great promise of the simple and most economical vitamin. The critical methyl-donor role of folate singularly emphasizes its therapeutic significance for almost all the chronic diseases of modern times which take root in phenotypes caused by epigenetic distortions. The significant benefit of folate–B12 supplement in obese diabetics reaped uniformly and rapidly in our referred study further endorses this and calls for renewed explorations to attain personalized medicine of folate in meeting the challenge of coronary artery disease.

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