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The effect of folate supplementation on systemic homocysteine plasma concentration and ocular blood flow in patients with diabetes

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Purpose

There is evidence that a folate deficiency – and as the biological consequence of the latter – higher homocysteine plasma levels are associated with an increased risk of vascular associated diseases.[1] For the eye, it has been shown that higher intake of folate reduces the risk of vascular related diseases such as age related macular degeneration.[2,3] Further studies suggest that decreased serum levels of folate and vitamin B12 may be an independent risk factor for diabetic retinopathy.[4] The reason for the association between low folate levels and the increased risk for vascular-associated ocular diseases is not entirely clear but may be at least partially related to an impairment of local blood flow regulation in these patients.
Consequently, the current study investigated the effect of a 3-month supplementation with folate on systemic homocysteine plasma levels in patients with diabetes. Further, ocular blood flow and endothelial function in the ocular microcirculation were assessed.

Methods

Twenty-four patients with diabetes received a dietary supplement containing 900 µg L-methylfolate (Ocufolin™ forte, Aprofol AG, Switzerland) for three consecutive months. The composition of the dietary supplement is shown in Table 1. The mean duration of diabetes in the study group was 14.6 ± 12.3 years. Plasma homocysteine concentration and retinal blood flow using a custom-built bi-directional Doppler OCT were assessed at baseline and after 3 months of folate intake. Flicker-induced retinal vasodilatation and retinal oxygen saturation was evaluated using a Dynamic Vessel Analyzer (IMEDOS, Jena, Germany). In addition, a standard ophthalmological examination was performed on both study days.

Ingredient	Amount
Folate (as (6S)-5-methyltetrahydrofolic acid, calcium salt)	900 µg
Vitamin C (Ca-Ascorbate)	45 mg
Vitamin D (as Cholecalciferol)	37.5 µg
Vitamin E Natural Tocopherols (as Alpha, Beta, Gamma, & Delta)	5 mg
Vitamin B1 (As Thiamine Hydrochloride) 1.5	1.5 mg
Vitamin B2 (Riboflavin)	10 mg
Vitamin B6 (as Pyridoxal-5-Phosphate)	3 mg
Vitamin B12 (as Methylcobalamin)	500 µg
Pantothenic Acid (as Calcium-D-Pantothenate)	5 mg
Zinc (as Zinc Acetate)	25 mg
Selenium (as L- Selenomethionine)	20 µg
Copper (as Cupric Gluconate)	667 µg
N-Acetyl Cysteine (NAC)	180 mg
Lutein	10 mg
Zeaxanthin	2 mg

Table 1: Composition of the dietary supplement.

References

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2. Christen, W.G., et al., Folic acid, pyridoxine, and cyanocobalamin combination treatment and age-related macular degeneration in women: the Women's Antioxidant and Folic Acid Cardiovascular Study. Arch Intern Med, 2009. 169(4): p. 335-41.
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4. Fotiou, P., et al., Vitamin status as a determinant of serum homocysteine concentration in type 2 diabetic retinopathy. J Diabetes Res, 2014. 2014: p. 807209.

Results

After three months, plasma homocysteine concentration significantly decreased from 14.2 ± 9.3 to 9.6 ± 6.6 µmol/L ($p < 0.001$, Figure 1a). In addition, a tendency towards an increase in total retinal blood flow from 36.8 ± 12.9 to 39.2 ± 10.8 µl/min was observed, but this effect did not reach the level of significance ($p = 0.11$, Figure 1b). Supplementation had no effect on retinal vessel diameters, retinal blood flow in single vessels, retinal oxygen saturation or flicker-induced vasodilatation or the response of retinal blood flow to flickering light. The corresponding values are given in Table 2.

	Study Day 1	Study Day 2	p-value
Arterial diameter (µm)	127.7 ± 18.1	126.7 ± 18.3	0.51
Venous diameter (µm)	159.3 ± 20.5	160.4 ± 22.1	0.46
Flicker response arteries (%)	2.4 ± 2.7	1.8 ± 3.3	0.46
Flicker response veins (%)	5.2 ± 3.2	3.7 ± 3.1	0.10
Arterial SaO_2 (%)	94.1 ± 3.2	94.7 ± 3.2	0.27
Venous SaO_2 (%)	74.3 ± 5.7	75.3 ± 6.0	0.24
A-V difference (%)	19.8 ± 4.9	19.4 ± 4.9	0.60

Table 2: Changes in assessed parameters after 3-months treatment (SaO_2... Oxygen saturation; A-V... Arteriovenous; IOP... Intraocular pressure). Data are presented as means ± SD)

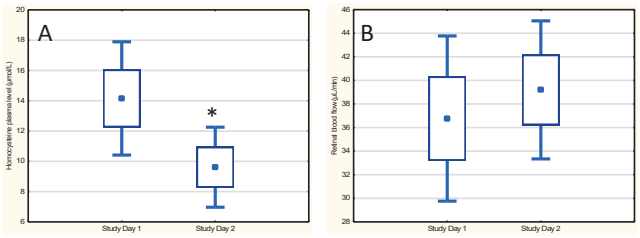

*Figure 1: (A) Plasma homocysteine levels and (B) total retinal blood flow on both study days. *significant vs. study day 1. Data are presented as means ± SD*

Conclusion

The present data show that a 3-months intake of a dietary supplement containing a moderate dose of folate is safe and capable of significantly reducing blood homocysteine levels in patients with diabetes. This is of special importance, since higher homocysteine plasma levels have been found to be associated with an increased risk of vascular associated diseases. Systemic folate supplementation also had a slight effect on retinal blood flow. Further studies on this parameter in larger cohorts should be performed.

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