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# The Role of Homocysteine and B Vitamins in Telomere Length: Results from the Cross-Sectional and Interventional Trials

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**Background:** Telomeres are essential for the maintenance of genomic integrity. Telomere length declines with age and telomere dysfunction has been proposed as a biomarker for age-related diseases. Vitamin B12, B6 and folic acid are essential cofactors for numerous cellular processes including the synthesis of purines and nucleotides, DNA and protein methylation. B vitamin deficiencies and hyperhomocysteinemiaare risk factors for the development of age-related diseases. The aim of this study is to evaluate the effects of B vitamins on telomere biology.

**Methods:** We analyzed the LURIC study (3316 cardiovascular patients), the Sud-Tyrolean study (STVS, 350 healthy subjects) and the KNOVIB study (60 elderly subjects were supplemented for one year with either vitamin B12, B6, folate, vitamin D and calcium (group A n=31) or only with vitamin D and calcium (group B n=29)). Relative telomere length (RTL), LINE-1 methylation, vitamin B6, B9, B12, homocysteine (HCY), 5-methyltetrahydrofolate (5-methylTHF), 5,10-methenylTHF, S-adenosylhomocysteine, S-adenosylmethionine (SAM), cystathionine, dimethyl-glycine, metylmalonic acid, choline, IL-6, C-reactive protein (CRP) and advanced glycation end-products (AGEs) were quantified.

**Results:**Median HCY was 9.8 µmol/L in the STVS and 12.4 µmol/L in the LURIC study. Age-corrected RTL correlated negatively with HCY (r=-0.151; p=0.007). RTL wasshorter in the presence of hyperhomocysteinemia. HCYwasalsolower in the highest (4th) quartile of age-corrected RTL. In the LURIC study,age-corrected RTL correlatedpositively with vitamin B6 (r=0.04; p=0.031), and the 4th quartile of age-corrected RTL wascharacterizedby higherlevels of vitamin B6 and folic acid and lowerlevels of IL-6 and hsCRP. Age-corrected RTL correlatednegatively with IL-6 (r=-0.043; p=0.019). IL-6 and hsCRPcorrelatednegatively with vitamin B6, folic acid, and positively with HCY.In the STVSage-corrected RTL correlatednegatively with AGEs (r=-0.146, p=0.01). AGEscorrelatedpositively with HCY and negatively with vitamin B12. In fact, AGEswerehigher in subjects with vitamin B12 below the median.

In the interventional study, at baseline HCY and 5-methylTHF were significant predictors of RTL. Vitamins supplementation decreased HCY in group A but not in group B. Vitamins supplementation in group A increased LINE-1-methylation but reduced it in group B. After supplementation in group B but not in group A LINE-1-methylation correlated inversely with RTL, and LINE-1-methylation variation was an independent predictor of RTL variations. In group B an increase in RTL was correlated with lower LINE-1-methylation.Subjects with 5-methylTHF >10nmol/L had compared with <10nmol/L at baseline lower LINE-1-methylation, due to a to a lower SAM formation. Subjects with HCY>12µmol/L had compared <12µmol/L at baseline and after supplementation longer telomeres. In group B subjects with HCY>12µmol/L had lower mean LINE-1-methylation. Multiple backward regression analysis showed, 5-methylTHF in group A and HCY in group B were significant predictors for LINE-1-methylation.