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One carbon metabolites and telomere length in cross-sectional, prospective and randomized one year B-/D-Vitamin supplementation trials

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 B_{12}, B_6 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 hyperhomocysteinemia are 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 South-Tyrolean study (STVS, 350 healthy subjects) and the KNOVIB study (60 elderly subjects were supplemented for one year with vitamin B_{12}, B_6, 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 was shorter in the presence of hyperhomocysteinemia. HCY was also lower in the highest (4th) quartile of age-corrected RTL. In the LURIC study, age-corrected RTL correlated positively with vitamin B6 (r=0.04; p=0.031), and the 4th quartile of age-corrected RTL was characterized by higher levels of vitamins B6 and folic acid and by lower levels of IL-6 and hsCRP. Age-corrected RTL correlated negatively with IL-6 (r=-0.043; p=0.019). IL-6 and hsCRP correlated negatively with vitamin B6, folic acid, and positively with HCY. In the STVS age-corrected RTL correlated negatively with AGEs (r=-0.146, p=0.01). AGEs correlated positively with HCY and negatively with vitamin B12. In fact, AGEs were higher 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.

Conclusions: The results from these studies provide evidence for an association between vitamin B_6, B_{12}, folic acid, HCY and telomere length. Hyperhomocysteinemia is able to negatively affect telomere length in healthy, in cardiovascular patients and in elderly. On one hand hyperhomocysteinemia is able to induce an inflammatory and oxidant status that in turn induces telomere attrition. On the other hand hyperhomocysteinemia induces DNA hypomethylation that in turn induces telomere dysfunction. In fact, literature data indicates that DNA hypomethylation is associated with elongated and dysfunctional telomeres. Further analyses are needed to confirm these results.

Biography

Wolfgang Herrmann is completed his Graduatation and Postgraduation from Saarland University and now he is working as Professor, He is also the president of the Technical University of Munich.

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