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Vascular wall and molecular markers of age in an ageing population

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Background and Aim: Atherosclerotic diseases is age-dependent phenotype but the evidence of the relationship between molecular markers of age and atherosclerosis is inconsistent. DNA methylation (DNAm) is known to change throughout the life course. The measure of 'epigenetic age' (EA) based on DNAm and leucocyte telomere length (LTL) are considered as ageing biomarker.

We investigated the relationship between EA, LTL and carotid intima-media thickness (CIMT) and plaques in serial measurements in a population sample of middle and older age in Russia.

Methods and Algorithms: A random population sample (Novosibirsk) was examined at baseline in 2003/05 (men, women, 45–69, n = 9360) and re-examined in 2015/18 (wave-3, 55–84, n = 3898). Carotid ultrasound and LTL measurement were conducted in a subsample at baseline and in wave 3 (773 at wave-1, 995 at wave-3, 526 have repeated measurements). We measured mean-mean CIMT on the far wall of both common carotid arteries and identified carotid plaques (CP) with high-resolution ultrasound. LTL was measured by real-time quantitative PCR-based method. The assessment of DNAm was conducted on Illumina EPIC850k Beadchip in a random subsample (94 subjects) and EA was calculated by Horvath.

Results: The mean follow-up period of serial measurements for carotid phenotypes was 7.5 years and 11.9 years for LTL. The mean CIMT was 0.75 (SD 0.18) mm at baseline and 0.91 (0.18) at wave-3 ($p < 0.001$); the average thickening rate was 0.03 (95 %CI 0.029–0.032) mm/year. The mean relative LTL was 1.35 (0.40) at baseline and 0.88 (SD 0.24) at wave-3 ($p < 0.001$), with average shortening rate of –0.043 (95 %CI –0.050; – 0.040) per year. The mean baseline EA was correlated with chronological age across the whole age range (r = 0.50, $p < 0.001$) and mean EA was higher compared to chronological age (65.1 years, SD 5.38 and 63.4 years, SD 3.02).

In cross-sectional analysis, at baseline there was no association between CIMT and LTL but in wave-3 LTL negatively correlated with CIMT in men (r = –0,130; p = 0,016).

In prospective analyses, among men baseline LTL inversely correlated with prospective CIMT, its increment during follow-up and thickening rate per year (p = 0.015–0.026). There was no association between baseline EA and prospective CIMT or CIMT thickening rate during follow-up.

For further analyses, a "progression of CIMT" was defined as increment larger than the mean increment during follow-up and contrasted with "no progression". Baseline LTL associated with CIMT progression (p = 0.028). In wave-3, the CIMT progression was more frequent in the 2nd and 3rd vs. 4th quartile of LTL (ordered smallest LTL quartile

to largest) in multivariable models (p = 0.032; 0.046). In addition, LTL in wave-3 was shorter in men with CP then in those without CP (p = 0.035, adjusted for age and smoking). Baseline EA was also associated with CIMT progression: the CIMT progression was more frequent in the 4th quartile vs 1st quartile of EA in multivariable logistic regression model (p = 0.041).

Conclusion: In a population sample of middle and elderly age, the age-related changes in carotid atherosclerosis and LTL were both of expected direction. At baseline, we did not detect cross-sectional associations between CIMT and LTL or EA. However, baseline LTL inversely correlated with prospective CIMT. Prospectively, among men shorter prospective LTL was independently associated with CIMT progression and with carotid plaques. Similarly, baseline EA was associated with progression of CIMT independently of other factors. The findings allow suggesting that the association between LTL shortening or epigenetic age and subclinical atherosclerosis might be confined to advanced vascular lesion.

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