Response by Benetos et al to letter regarding article: "Short leukocyte telomere length precedes clinical expression of atherosclerosis: The blood-and-muscle model"

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Letter to the Editor

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Response by Benetos et al to Letter Regarding Article, "Short Leukocyte Telomere Length Precedes Clinical Expression of Atherosclerosis: The Blood-and-Muscle Model"

In Response:

Converging evidence suggests that the hematopoietic system is a key player in the telomere length (TL)–atherosclerosis connection. The hematopoietic system and the vascular endothelium, where atherosclerosis begins, share a common embryonic precursor—the hemogenic endothelium, which gives birth not only to the vascular endothelium but also to hematopoietic stem cells that build the hematopoietic system.[1] This shared embryonic history and perpetual interactions between the hematopoietic system and the vascular endothelium prompted the proposal to unite the 2 systems into a singular entity coined the hemothelium.[2] We draw on the hemothelium paradigm in responding to the letter by De Meyer about the meaning of the findings presented in our article.[3]

De Meyer rightfully focuses on the vascular endothelium as a key player in the TL–atherosclerosis connection but provides little evidence to support his idea that as expressed in leukocyte TL (LTL), the hematopoietic system has a minimal role in this connection. To build his case, De Meyer cites a study showing shorter TL in vascular endothelial cells from 11 patients who died from atherosclerotic cardiovascular disease (ACVD) than that in 22 individuals who died from other causes with no TL overlap between the 2 groups and between endothelial cells derived from atherosclerotic regions than nonatherosclerotic regions in the coronary arteries.[4] He notes, in contrast, that although LTL is slightly shorter in patients with ACVD than in their peers without the disease, there is considerable overlap between the 2 groups. De Meyer considers the lack of TL overlap in vascular endothelial cells between patients with ACVD and controls as evidence that the TL–atherosclerosis connection originates at the level of the vascular endothelium and that the hematopoietic system plays little or no role. We express skepticism about the observed complete partition, that is, no overlap in vascular endothelial cell TL between patients with ACVD and controls based on data generated using suboptimal TL measurements (dot blots of the ratio of telomere/centromere signals) in a tiny sample.[4] What's more, the finding is incompatible with the polygenetic features of TL and ACVD, both of which are complex genetic traits, that is, they are outcomes of numerous interacting factors, genetic and environmental, that produce wide variation with overlaps between patients and controls.

While TL is a complex genetic trait, highly deleterious mutations in TL maintenance genes may result in rare monogenic diseases, marked by extremely short telomeres that clearly set apart TL in patients with the diseases from TL in other individuals across the population. De Meyer notes that patients with one of these diseases, dyskeratosis congenita (DC), are not prone to ACVD. He argues that DC is a bone marrow disease. Therefore, the lack of display of ACVD in patients with the disease is proof that the hematopoietic system has little or no role in the LTL–atherosclerosis connection. However, the mutations, and hence critically short TL, in DC impact not only the hematopoietic system but also all tissues, including the vascular endothelium. Therefore, according to De Meyer's hypothesis, patients with the disease should experience atherosclerosis. The most plausible explanation that patients with DC do not display ACVD is their age. While the clinical manifestations of ACVD, an aging-related disease, largely unfold in middle-age and elderly people, individuals with DC typically succumb to bone marrow failure and other complications of their disease at a young age.

Genome-wide association studies have identified LTL-associated SNPs (single nucleotide polymorphisms) mapped to genetic regions, some of which harbor TL maintenance genes. These SNPs have been used to construct genetic risk scores for short LTL that predict increased risk of ACVD. De Meyer points out that one of these SNPs, mapped to *NAF1*, is associated with a longer rather than shorter LTL in patients with ACVD. Such a finding underscores the thesis that ACVD is a complex genetic trait, where multiple genes interact mutually and with the environment through different pathways. Thus, the relation between these genes and ACVD might be mediated through mechanisms that are not always apparent. He further suggests that the LTL–atherosclerosis connection predicted by these genetic risk scores might reflect LTL-maintenance genes, promoting a faster TL attrition during early life rather than having constitutively short TL at birth. The association between TL maintenance genes and ACVD has to do with TL dynamics stemming from somatic cell replication. The most intense cell replication takes place in utero, where the union of egg and sperm gives birth to a newborn comprising tens of trillions of cells. This is the period where these genes are likely to leave their principal marks on TL in all tissues. However, we do not dismiss the possibility that De Meyer raises regarding early, postnatal life.

Which brings us back to the hemothelium. TL is highly variable across individuals but similar within somatic tissues of the individual. Still, TL does differ across these tissues, largely reflecting their replicative history (and remaining replicative potential). In our study, we have used muscle TL as a scaling factor to offset the wide interindividual variation in TL across individuals and as an indicator of TL in early life. Our findings that variation in LTL and not muscle TL explains the association between the blood–muscle TL gap and ACVD point to TL dynamics in the hemothelium as a player in the development of atherosclerosis.

Finally, there is no model agreed upon by all researchers to explain the TL–atherosclerosis connection. The traditional explanation of the association of short LTL with ACVD is that inflammation and oxidative stress, the hallmarks of atherosclerosis, heighten the rate of LTL attrition, and, therefore, a short LTL is a biomarker of this and other aging-related diseases. This explanation, which attributes no causal role of TL in ACVD, overlooks vascular repair, the other key component in vascular homeostasis. This repair is mediated in part by progenitor cells dispatched from

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the bone marrow to areas of vascular injury. Although questions have been raised regarding the exact nature of these cells and in what way they engage in vascular repair, the weight of the evidence is tilting toward the notion that these cells do partake in vascular repair. The association of LTL with the number of these cells and their independent associations with ACVD[5] are consistent with the concept that atherosclerosis is a complex trait that reflects in some measure TL dynamics in the hemothelium. The hemothelium paradigm recognizes the hematopoietic system and the vascular endothelium as partners in vascular health and disease.

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Disclosures

None.

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