Epidemiological studies have identified hypertension (HT) as one of the most important risk factors for cardiovascular events. Blood pressure (BP) levels are strong predictors of cardiovascular events. However, at an individual level there is wide variation regarding the association between cardiovascular events and HT, even in individuals with the same BP levels. HT is a modifiable risk factor, but there are some risk factors that cannot be changed. HT or cardiovascular events become increasingly common with advancing age; however, there is also wide variation in the association between HT or cardiovascular events and the age of manifestation. In other words, there is a difference between chronological age and biological age.

Leukocyte telomere length provides a marker for biological age, at least at the cellular level, with shorter telomeres indicating a biological age greater than an individual’s chronological age. In addition, shorter telomere length has been reported to be associated with severe coronary artery disease, heart failure, and a higher mortality rate of heart disease. Although the telomere length is definitely a risk marker for heart disease, with studies consistently associating shorter telomere lengths with increased risk, the association between shorter telomere length and risk, which appears to be further modulated by age, is still not clear.

In this issue of the Journal, Zhang et al examine the possibility that homocysteine causes shorter telomere length. Many studies have shown that there is an independent and graded association between homocysteine levels and cardiovascular risk, and the homocysteine level itself had been reported to cause oxidative stress and damage to the endothelium. After adjusting for confounding risk factors, Zhang et al indeed found that a person’s homocysteine level was independently and inversely associated with telomere length. This result supports the potential role of oxidase stress induced by an elevated homocysteine level as the cause of shorter telomeres, because increased oxidant stress has been shown to increase rates of telomere attrition in vitro. In addition, Zhang et al report that folate status was associated with a reduction of the effect of homocysteine for short telomere length, and an increased folate level alone can reverse the effect of homocysteine. However, more attention should be paid to how this conclusion was achieved. Although folic acid and vitamin B supplementation are thought to be the most important dietary determinants of homocysteine, and the HOPE (Heart Outcomes Prevention Evaluation) 2 study was performed to investigate whether a supplement combining folic acid with vitamin B could reduce the risk of major cardiovascular events in 5,552 patients with vascular disease, the active treatment group did not show significantly decreased risk of cardiovascular death compared with the control group, even though the homocysteine level in the active control group decreased. The WOSCOPS (West of Scotland Primary Prevention Study) compared 484 patients with coronary artery disease (CAD) and 1,059 controls without. Although the degree of decrease in mean telomere length with age showed the same trend in the 2 groups, this study showed that those with shorter baseline telomeres had a significantly higher risk of developing subsequent CAD and this increased risk with...
shorter baseline telomeres was attenuated in individuals receiving treatment with a statin, although this association was not found in the patients with longer baseline telomeres. That study indicated that the association of shorter telomeres with CAD was not a consequence of the disease. Thus, telomere length itself is not treatable risk factor, but it could be useful for predicting the response to other treatable risk factors in terms of cardiovascular protection. Actually, in a post hoc analysis of the VISP (Vitamin Intervention for Stroke Prevention) trial, among individuals older than 67 years, high-dose vitamin therapy was associated with reduced risk of recurrent stroke, although this association was not found among individuals younger than 67 years. Hence, the effect of vitamin supplementation might differ according to age. However, it is not clear whether the intervention for homocysteine based on telomere length is beneficial or not. Another concern of the study reported by Zhang et al is that they did not evaluate smoking status. When we previously investigated the effect of smoking and HT on plasma homocysteine in 133 community-dwelling Japanese populations, hypertensive smokers had the highest homocysteine levels subclassified into 4 groups by smoking and HT status. An intervention for homocysteine based on telomere length might be of more benefit in smokers than in non-smokers (Figure 1).

BP level is used in the management of HT, because it is a treatable risk factor of cardiovascular events. Recently, BP variability assessed by clinic and out-of-clinic BP measurement was associated with organ damage and cardiovascular outcome independent of BP level. However, there is no evidence as to whether an intervention for BP variability would be more associated with a reduction in progressive organ damage or cardiovascular events than that for BP level. Guidelines show the relevance of HT as a risk factor in relation not only to the magnitude of the BP level, but also in terms of the so-called total cardiovascular risk resulting from the coexistence of high BP with conventional risk factors including age. This may also be the case for BP variability and a new factor (ie, telomere length-related homocysteine) (Figure 2). Physicians should control risk factors, taking into account their inter-individual variation.

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References