Total Cholesterol, Severity of Stroke, and All-Cause Mortality

To the Editor:

The association of blood cholesterol with the risk of stroke, a very important clinical and public health issue, appears to be in dispute. To fuel the debate, Olsen et al1 reported a study of 513 patients admitted in a Copenhagen, Denmark hospital with acute ischemic stroke. All study data, including measures of total serum cholesterol (TSC) and the severity of stroke, were collected on admission in the hospital, and poststroke 10-year all-cause mortality was ascertained. The severity of stroke was measured by the Scandinavian Stroke Scale that is based on a composite of neurological deficits, and severity was found to be correlated with the cerebral infarct size seen on CT scans. The authors found that poststroke TSC levels were inversely associated with the severity of stroke, cerebral infarct size, and mortality, which were adjusted for the covariates.1

The authors concluded that “hypercholesterolemia primarily is associated with minor strokes due to small-vessel occlusion”. Their conclusion contradicts the well established role of cholesterol in the pathogenesis of atherosclerosis including that of cerebral and precerebral vessels. Ischemic stroke is predominantly caused by macrovascular disease, not microvascular. The findings of this study1 are unreliable and misleading simply because poststroke TSC levels are not representative of the levels before the onset of the arterial disease. Cross-sectional data cannot establish the temporal relationship between TSC and the risk of severe ischemic stroke. Only measures of TSC in apparently healthy subjects should be used to determine the effect of cholesterol on the risk of ischemic stroke, its severity and associated mortality.

It may be that significant cerebral and/or precerebral arterial disease that could have resulted in a severe stroke or extensive infarct produced signs and symptoms that alerted physicians to initiate cholesterol-lowering therapy before stroke. It may also be that, somehow, severe stroke or extensive cerebral infarction has greater effect on blood chemistry including TSC at the acute stage than a mild or small stroke. There is some evidence of TSC decreasing during the acute stage of stroke2 (and Reference 27 in the article1). Another good example of distortion of cholesterol-stroke association was a study of hospitalized patients with acute ischemic stroke, which found inverse associations of poststroke TSC, HDL-cholesterol, and LDL-cholesterol levels with the risk of stroke.3

In the Framingham (cohort) Study, the risk of atherosclerotic carotid stenosis, a precursor of ischemic stroke, was significantly associated with high TSC levels measured 8 years before the diagnosis.4,5 However, there was no association between carotid stenosis and TSC measured at the time of diagnosis.5 The researchers concluded that “there is a time lag between the observation of an elevated cholesterol level and its expression as an increased degree of carotid atherosclerosis”.4 The longer the interval between measuring cholesterol and the diagnosis of first stroke, the more reliable is the association. Olsen et al1 cited 5 studies (References 7 to 11 in their article) that allegedly showed conflicting evidence of association between cholesterol and the risk of stroke. One of these studies was a meta-analysis of data for 45 cohorts at risk of all types of stroke combined. Out of the remaining 4 prospective cohort studies, 1 did not find any association and 3 studies found positive association between baseline TSC and subsequent ischemic stroke. It should be of interest to mention that a prospective study of a cohort of Copenhagen citizens, conducted at the same hospital where Olsen et al study1 patients were admitted, found a positive association between baseline TSC and the risk of subsequent nonhemorrhagic stroke.6 Not cited by Olsen et al were 3 additional prospective cohort studies that found positive association between baseline TSC and ischemic stroke.7–9

In their study, Olsen et al1 found that 86% of all deaths were caused by stroke or heart diseases. In support of their finding of an inverse association between poststroke TSC and all-cause mortality, Olsen et al cited 3 studies (References 17 to 19 in their article) with similar findings. However, they did not state that these 3 studies were also hospital-based cross-sectional studies: that is, they used poststroke measures of TSC. They also did not cite several prospective cohort studies that found positive association between pre-stroke TSC and all-cause mortality.10,11

In conclusion, data on cholesterol levels measured after the onset of stroke should not be used for studies of the risk factors for severity of stroke or poststroke mortality. There may be an inverse association of cholesterol with severity of stroke or mortality, but this study1 was not capable of reliably determining any association.

Disclosures

None.

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