Serum Albumin Level as a Predictor of Ischemic Stroke Outcome

To the Editor:

We read with great interest the recent article by Dr Dziedzic et al1 on the relationship between serum albumin level and ischemic stroke outcome. Even though low serum albumin has been associated with an increased incidence of stroke in epidemiologic studies,2 a high serum albumin level in acute stroke patients was described, for the first time, to decrease the risk of poor outcome among hospitalized patients. The neuromodulatory effects of endogenous albumin on the capillary microcirculation in the early reperfusion phase were proposed to explain the cellular mechanism of this association, and the role of exogenous albumin therapy in stroke recovery was briefly reviewed.

It is important to recognize the role of serum albumin as a marker of clinical outcomes in vascular disease. Apart from stroke, serum albumin has been associated with adverse vascular events in patients with cardiac3 and renal4 diseases. Among hospitalized patients, hypoalbuminemia was found to be associated with frequent hospitalizations, higher mortality, and readmission,5 and an independent prognostic factor for all deaths among healthy middle-aged individuals in population studies.6 Serum albumin is regulated by factors influencing protein synthesis, breakdown, leakage to the extravascular space, and food intake. In clinical practice, serum albumin is often considered a marker of nutritional status and a negative phase protein that decreases in concentration during injury and sepsis.7

There has been conflicting evidence in the literature on albumin therapy in treating patients with hypoalbuminemia from an underlying vascular disease. Albumin has a molecular weight of about 66 kDa, thus preventing it from passing through the blood–brain barrier by diffusion or by carrier systems through these membranes. Local redistribution, crystalloid dilution, and changes in the metabolism of albumin, which result in ineffective delivery and concentration within the central nervous system, frustrate therapeutic interventions. In septic patients, albumin therapy was not associated with a rise in serum albumin. Instead, a fall in serum albumin was observed and this was hypothesized to be secondary to capillary leakage.8

Until these important questions on albumin therapy are answered in randomized controlled studies, therapeutic options in patients with hypoalbuminemia should be directed toward treating the underlying cause, avoiding or treating salt and water overload, instituting prompt medical and surgical treatment of inflammation and sepsis, and providing appropriate nutritional support to enhance recovery in patients with ischemic strokes.

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Response:

We thank Dr Seet and colleagues for their thoughtful comments to our article. We agree that hypoalbuminemia appears to be a predictor of poor prognosis in different clinical settings and even in apparently healthy individuals.1 It is still unknown in which way hypoalbuminemia can impair the prognosis. The mechanisms responsible for this phenomenon are not limited to energy depletion only, but can be also related to impaired immune and endothelial response, as well as extracellular water expansion.2 On the other hand, experimental studies revealed a beneficial effect of albumin infusion in animal models of cerebral ischemia and it was suggested that this neuroprotective effect is mediated by multiple specific actions of albumin including antioxidative properties, influence on endothelial functions, and venular perfusion.3,4 Which of the above-mentioned mechanisms of albumin action are relevant to human stroke remains to be established.

Albumin belongs to negative acute phase proteins. In our study we measured albumin level within 36 hours after stroke onset. We can’t exclude that acute phase response accompanying ischemic stroke can to some degree decrease albumin level in this time period. Inflammatory reaction defined as C-reactive protein level was found to be the most pronounced 3 to 7 days after stroke onset.5 Davalos et al found fall in albumin concentration between day 1 and day 7 of stroke (40.7 ± 4.6 versus 39.5 ± 5.3 g/L) with borderline statistical significance (P = 0.05).6 Other authors observed significant decrease in albumin level 2 and 4 weeks after stroke onset and this phenomenon couldn’t be explained by acute phase reaction.7 Unfortunately there is a lack of studies investigating changes in serum albumin level during acute phase of stroke.

Could albumin infusion be beneficial in human stroke? We share some concerns of Dr Seet and colleagues that this form of the therapy could be ineffective. However, we think that promising results of animal studies warrant the attempt to conduct clinical trials. In our opinion, 2 issues can be addressed in clinical studies: first, if correction of hypoalbuminemia (if possible) can influence the stroke outcome; second, if albumin infusion in early stroke in patients with normoalbuminemia can be beneficial as shown in animal models.

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Association Between Pulse Pressure Values During the Acute Stroke Stage and Stroke Outcome

To the Editor:

We read with great interest the recent Research Report by Aslanyan et al.1 The authors reported that elevated weighted average pulse pressure (PP) during the first 60 hours of ischemic stroke was independently associated with poor outcome assessed by mortality, Barthel index, National Institutes of Health Stroke Score and modified Rankin score. Elevated baseline PP was associated with Barthel Index and Rankin score but not with mortality. Weighted average PP was the only blood pressure (BP) component to be consistently associated with all outcome measures.

We have also evaluated the prognostic value of the different BP components in 198 patients with acute stroke (146 cases with cerebral infarction and 42 cases with intracerebral hemorrhage) by means of 24-hour BP-monitoring.2 Our results indicated an independent association between increasing 24-hour PP levels and 1-year mortality after correcting for stroke risk factors, stroke subtypes, clinical (stroke severity and level of consciousness) and radiological characteristics (brain edema, mass effect and hemorrhagic transformation). Higher PP levels on hospital admission were related to an increased risk of 1-year mortality on univariate analysis, but in the multivariate Cox-regression model this association did not retain its statistical significance. This finding underlines the superiority of 24-hour BP variables over admission BP measurements in predicting stroke outcome. It is in keeping with the results of Aslanyan et al and other investigators, which indicate that variables describing BP course during the acute stroke period, such as 24-hour,2,3,4 beat-to-beat5 and weighted average1 BP recordings correlate more strongly and independently with stroke outcome.

On the other hand, other studies failed to document any association between PP levels in acute stroke and early6 or late outcome.4 Since, antihypertensive medication have been shown to have a differential effect on conduit vessel stiffness and to selectively alter the different BP components,6–8 we believe that the prognostic impact of PP levels at baseline and especially during the first hours of ictus on stroke outcome needs further clarification. An increasing body of evidence suggests that raised BP levels following acute stroke may not be a benign phenomenon and are associated with adverse prognosis.9 However, before embarking in a large randomized, placebo-controlled trial the question of whether the lowering of the pulsatile, the steady or both BP components in acute stroke might improve outcome remains to be answered.

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Does Preventing Stroke Prevent All Kinds of Dementia?

To the Editor:

The recent publication in Stroke regarding dementia after stroke4 makes interesting observations. However, there are some points in the article to which I would like to draw attention.

First, the subgroup analysis in the text mentions that the e4 allele for apolipoprotein E (ApoE) genotype was present in 17.3% of the cases and in 22% of the controls. Table 1 in the article seems to have a printing error in that the above percentages have been reversed in the table (ie, 22% of cases and 17% of controls have e4 allele for ApoE genotype).

Second, the changing denominators in Table 1 show that a lot of baseline data were actually missing. A mention of this would have been appropriate in the limitations of the study.

Last, it seems logical to conclude that the prevention of stroke would reduce the burden of vascular dementia. The authors conclude that primary and secondary prevention of stroke should significantly decrease the risk of all dementia. I wonder how valid that observation could be. It is true that a proportion of stroke cases had Alzheimer disease (AD), but the proportion of AD still remained higher among controls. There is no statistical