Hyperinsulinemia and Estrogen-Deficiency as Risk Factors for Stroke in Women

To the Editor:

We read with great interest the recent article by Dr. Ho and colleagues dealing with the relationship between diabetes and stroke mortality in women. The results of their study demonstrated that women with diabetes mellitus and no prevalent cardiovascular diseases (CVD) had a 3-fold-increased fatal stroke risk compared with nondiabetic women without CVD. They proposed that, although stroke mortality was highest among women with prior stroke, diabetes carries a fatal stroke risk similar to that of a history of prior stroke and may warrant more aggressive treatment strategies in the future prevention of stroke.

Numerous studies have already shown a role of hyperinsulinemia in the pathogenesis of vascular complications in circulatory disorders. Sela et al demonstrated that polymorphonuclear leukocytes (PMN) in essential hypertension showed increased level of intracellular calcium content correlating positively with the individual’s blood pressure and plasma insulin. They proposed that, because PMN priming may lead to oxidative stress and inflammation, intracellular calcium and insulin are involved in the pathogenesis of hypertension-induced vascular injury. In a study we presented earlier, a relationship between membrane fluidity (a reciprocal value of membrane microviscosity) and erythrocytes and insulin was investigated in essential hypertension by means of an electron paramagnetic resonance method.

The membrane fluidity of erythrocytes was significantly lower in patients with essential hypertension than in normotensive subjects. In addition, it was demonstrated that the higher the plasma insulin level, the lower the membrane fluidity of erythrocytes, which might indicate that hyperinsulinemia might be involved in the regulation of membrane fluidity of erythrocytes in essential hypertension.

In an in vitro study, we showed that insulin alone and in combination with calcium decreased membrane fluidity of erythrocytes. The decreased membrane fluidity of erythrocytes might cause a disturbance in the blood rheologic behavior and the microcirculation, which could contribute, at least in part, to pathogenesis of circulatory disorders. One hypothesis is that insulin might accelerate abnormalities in intracellular calcium metabolism and membrane function in blood cells such as PMN and erythrocytes, which could partially explain the vascular complications in subjects with hyperinsulinemia.

In contrast, we demonstrated that estrogen (17β-estradiol) increased membrane fluidity of erythrocytes and improved the rigidity of cell membranes in postmenopausal women via a nitric oxide (NO) and cyclic guanosine 3',5'-monophosphate (cGMP)-dependent mechanism. In the separate series of experiments, we showed that hormone replacement therapy restored the membrane microviscosity in elderly women with a concomitant increase in plasma NO metabolite level. It is possible that insulin and estrogen may exert opposite effects on membrane microviscosity of erythrocytes, although the precise mechanism underlying their modulatory effects on the membrane function is still uncertain. In this context, we speculate that both hyperinsulinemia and estrogen-deficiency could cause a disturbance in the blood rheologic behavior and the microcirculation. These abnormalities may induce vascular complications in women. It would be necessary to assess more precisely the roles of hyperinsulinemia and estrogen-deficiency and their contribution to the risk for stroke in women.

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