Hyperinsulinemia, Hyperleptinemia, and Nitric Oxide in the Regulation of Membrane Micoviscosity

To the Editor:

We read with interest the article by Dr Piatti and colleagues1 dealing with the relationship between hyperinsulinemia, hyperleptinemia, and nitric oxide (NO) in patients with restenosis after coronary stenting. The results of their study demonstrated that among the stented patients, insulin and leptin levels were higher in those with restenosis than in those without restenosis. In addition, NO release during an oral glucose tolerance test was blunted in patients with restenosis. The authors proposed that insulin resistance and endothelial dysfunction were independent predictors of early restenosis after coronary stenting.

There is evidence that insulin might actively participate in the regulation of membrane function. Sela et al2 demonstrated that polymorphonuclear leukocytes (PMN) in essential hypertension showed increased 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,3,4 a relationship between membrane fluidity (a reciprocal value of membrane microviscosity) of erythrocytes and insulin was investigated in essential hypertension by means of an electron paramagnetic resonance method. We demonstrated that the higher the plasma insulin level, the lower the membrane fluidity of erythrocytes. This might indicate that hyperinsulinemia is involved in the regulation of membrane fluidity of erythrocytes. In an in vitro study, we showed that insulin alone and in combination with calcium decreased the 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 the pathophysiology 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. On the other hand, it was demonstrated that leptin increased the membrane fluidity of erythrocytes and improved the rigidity of cell membranes via the NO- and cGMP-dependent mechanism,5 suggesting that insulin and leptin may exert opposite effects on membrane microviscosity of erythrocytes. In this context, we speculate that hyperinsulinemia and insufficient leptin-induced NO production could coordinate modulate the membrane function in patients with restenosis. It would be necessary to assess more precisely the functional interactions between insulin and leptin in the regulation of membrane microviscosity and their contribution to the mechanism underlying restenosis after coronary stenting.

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Response

We thank Drs Tsuda and Nishio for their comments regarding our recently published data.1 Drs Tsuda and Nishio speculate that hyperinsulinemia and insufficient leptin-induced nitric oxide (NO) production could regulate membrane microviscosity of erythrocytes and this might be a mechanism of restenosis after coronary stenting. This hypothesis was derived from our data that among the stented patients, insulin and leptin levels were higher in those with restenosis than in those without restenosis. In addition, NO release during an oral glucose tolerance test was blunted in patients with restenosis.1

Previous data of Dr Tsuda et al2 demonstrated that, in the presence of hyperinsulinemia, membrane fluidity (a reciprocal value of membrane microviscosity) of erythrocytes was significantly decreased in essential hypertension. In addition, they showed that insulin alone and in combination with calcium decreased the membrane fluidity of erythrocytes.2 Their hypothesis is that insulin might impair intracellular calcium metabolism and membrane function in blood cells, partially explaining the vascular complications in subjects with hyperinsulinemia. The knowledge that hyperinsulinemic states and type 2 diabetes are associated with impaired erythrocyte deformability is not new, but its clinical importance was never entirely defined. Furthermore, the effects of abnormal erythrocyte deformability observed in hyperinsulinemic states are assumed to be greater on small vessels (eg, retinal vessels) than on large vessels (eg, branches of coronary arteries).

The role of leptin in cardiovascular and cerebrovascular disease is actually under investigation. We reported a negative correlation between leptin levels and the area under the curve of the incremental (above basal) NOx excursion during the OGTT, calculated using the trapezoidal method,1 supporting previous data suggesting that chronic hyperleptinemia might reduce NO synthesis because of the increased oxidative stress in endothelial cells. This might be a new mechanism of vascular disease. However, the effects of leptin are not always univocal, as reviewed in reference 3. It is known that leptin induces proliferation, differentiation, and functional activation of vascular smooth muscle cells, endothelial cells, and, possibly, circulating peripheral blood cells, contributing to neointima formation after severe vascular injury. However, the effect of leptin on endothelial cells (enhanced proliferation, increased survival) and angiogenesis suggest potential beneficial effect of leptin on vascular wall. To reconcile these data, Werner et al3 suggested that hyperleptinemia per se might not have detrimental effects on the vascular wall until concomitant abnormalities develop, such as metabolic syndrome and insulin resistance.

On the other hand, Tsuda et al demonstrated that leptin increased the membrane fluidity of erythrocytes and improved the rigidity of cell membranes via the NO- and cGMP-dependent mechanism,4 suggesting that insulin and leptin may exert opposite effects on membrane microviscosity of erythrocytes. The hypothesis of Drs Tsuda and Nishio of a modulation of hyperinsulinemia and insufficient leptin-induced NO production on membrane microviscosity in patients with restenosis is inter-

estingly, but we are not aware of any research dealing with impaired erythrocyte deformability or viscosity as an alternative mechanism underlying restenosis after coronary stenting. In our opinion, a possible mechanism relating erythrocyte deformability and in-stent restenosis might be through an impairment of shear stress. Recently, Carlier et al⁵ provided direct evidence for an important modulating role of shear stress in in-stent neointimal hyperplasia. However, we believe that other mechanisms are more important in the process of restenosis after coronary stenting.

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