

COMMENTARY

Matrix metalloproteinases: keys to healthier blood vessels in diabetes?

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Abstract

In this issue of *Journal of Endocrinology*, Schuyler *et al.* show that intimal lesions in atherosclerosis-prone diabetic *apoE*^{-/-} mice are reduced by insulin treatment. An increase of metalloproteinase-9 expression was observed in untreated diabetic *apoE*^{-/-} mice; this was absent in insulin-treated

mice. The study suggests that hindering of tissue-remodeling metalloproteinases may account for the beneficial effects of proper metabolic control in patients with diabetes. This clinically relevant finding prompts further exploration.

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The fact that type 2 diabetes has become pandemic is difficult to escape. Increased morbidity and mortality in cardiovascular events, which frequently accompany the disease, are the most severe consequences of the diabetes pandemic. This problem is caused by an acceleration of atherosclerosis in patients with diabetes. In fact, it has become apparent that glucose intolerance or frank diabetes occurs in up to three of four patients with acute myocardial infarction, even if these patients have not previously been diagnosed with diabetes (Anselmino *et al.* 2010). This notwithstanding the cause of accelerated atherosclerosis in diabetes is not fully understood. Although inflammation now has been implicated in impairment of insulin sensitivity (Shoelson *et al.* 2007) and perturbation of insulin secretion (Dinarello *et al.* 2010) in type 2 diabetes, it is not clear whether inflammatory processes, known to play an important role in atherosclerosis, are exaggerated in the vessel wall of patients with diabetes. Toxic effects of elevated plasma glucose as well as circulating lipids, known as glucotoxicity and lipotoxicity, respectively, may be precipitating or potentiating factors. Epigenetic changes in the vascular wall have also been implicated in the advent of the vascular complications of diabetes (El-Osta *et al.* 2008). All these notions agree with the fact that improved glycemic control significantly reduces the late complications of any type of diabetes, and this includes cardiovascular disease.

In this issue of *Journal of Endocrinology*, Schuyler *et al.* (2011) provide new insights into the pathogenesis of atherosclerosis in diabetes. They hypothesized that enhanced plaque stability could account for the beneficial effects of improved glycemic control on cardiovascular

complications in diabetes. The authors were particularly interested in matrix metalloproteinases (MMP), which are a family of zinc-dependent endopeptidases. These enzymes degrade extracellular matrix components and may hence remodel vascular tissue and affect plaque stability (Galis & Khatri 2002). For their studies, they used *apoE*^{-/-} mice that are a well-established murine model for atherosclerosis. The mice were made diabetic by streptozotocin, a cytotoxic agent that selectively kills the insulin-producing β -cells. Then, the hyperglycemic *apoE*^{-/-} mice were treated with insulin and compared with untreated as well as non-diabetic *apoE*^{-/-} mice and with an unrelated mouse line, C57BL/6. As expected, insulin treatment lowered plasma glucose levels. Interestingly, plasma cholesterol levels were higher in diabetic *apoE*^{-/-} mice, and this elevation was hindered by the insulin treatment. When analyzing aortic plaques, the intimal size directly reflected glycemic control: plaques were greatest in the untreated diabetic *apoE*^{-/-} mice. This was further paralleled by increased MMP9 expression, as assessed both by immunocytochemistry and by quantitative real-time PCR. However, the expression of MMP2 and MMP13 remained unchanged in the untreated diabetic *apoE*^{-/-} mice, implying that insulin treatment selectively affected MMP9. Finally, interleukin 6 (IL6) is a known regulator of MMP9 and has previously been implicated in inflammatory changes in type 2 diabetes (Pedersen 2009). The authors found that expression of IL6 was increased in the untreated diabetic *apoE*^{-/-} mice, an increase that was attenuated by insulin secretion. This provided a possible mechanism for the protection against plaque growth by insulin and MMP9. Of note, insulin

treatment did not reduce macrophage content in the plaques of insulin-treated *apoE^{-/-}* mice.

The interesting findings by Schuyler *et al.* raise some important questions. In the studies, plasma glucose levels differed among the groups of mice. Therefore, it is difficult to know, based on the present data, whether the beneficial effects in the treated mice can be attributed to insulin itself or to the amelioration of the metabolic perturbation, i.e. plasma glucose and cholesterol, both of which were reduced by insulin. This is a clinically relevant question because in type 2 diabetes, hyperglycemia can be treated in several ways. One way of testing this possibility is treatment of diabetic *apoE^{-/-}* mice with phlorizin, a drug that increases renal excretion of glucose. Also, in the model studied by the authors, insulinopenia was induced by a destruction of β -cells. In many patients with type 2 diabetes, there is hyperinsulinemia. Thus, testing the concept of MMP9 and plaque stability could be of interest in an animal model for type 2 diabetes. This could also resolve whether it is the actual lack of insulin that allows increased expression of MMP9. Moreover, *in vitro* studies in endothelial and smooth muscle cells of the regulation of MMP9 expression would be helpful. Nevertheless, the study by Schuyler *et al.* should inspire further investigation of this interesting and clinically important phenomenon.

Declaration of interest

The author declares that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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References

- Anselmino M, Malmberg K, Mellbin L & Rydén L 2010 Overview of the importance of glycaemic control for cardiovascular events in the in-and out-patient setting. *Reviews in Endocrine and Metabolic Disorders* **11** 87–94. (doi:10.1007/s11154-010-9136-2)
- Dinarello CA, Donath MY & Mandrup-Poulsen T 2010 Role of IL-1beta in type 2 diabetes. *Current Opinion in Endocrinology, Diabetes, and Obesity* **17** 314–321. (doi:10.1097/MED.0b013e32833bf6dc)
- El-Osta A, Brasacchio D, Yao D, Poci A, Jones PL, Roeder R.G, Cooper ME & Brownlee M 2008 Transient high glucose causes persistent epigenetic changes and altered gene expression during subsequent normoglycemia. *Journal of Experimental Medicine* **205** 2409–2417. (doi:10.1084/jem.20081188)
- Galis ZS & Khatri JJ 2002 Matrix metalloproteinases in vascular remodeling and atherogenesis: the good, the bad, and the ugly. *Circulation Research* **90** 251–262.
- Pedersen BK 2009 The diseasome of physical inactivity – and the role of myokines in muscle – fat cross talk. *Journal of Physiology* **587** 5559–5568. (doi:10.1113/jphysiol.2009.179515)
- Schuyler CA, Ta NN, Li Y, Lopes-Virella MF & Huang Y 2011 Insulin treatment attenuates diabetes-increased atherosclerotic intimal lesions and matrix metalloproteinase-9 expression in apolipoprotein E-deficient mice. *Journal of Endocrinology* **210** 37–46. (doi:10.1530/JOE-10-0420)
- Shoelson SE, Herrero L & Naaz A 2007 Obesity, inflammation, and insulin resistance. *Gastroenterology* **132** 2169–2180. (doi:10.1053/j.gastro.2007.03.059)

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