Aneurysms and Diabetes Mellitus: A Strange Symbiosis?

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The incidence of diabetes mellitus (DM) is rising and at the same time the incidence of aneurysms is for various reasons declining. The study by Patel et al. [1] presented a very well written and comprehensive review regarding the proposed inverse association between DM and aneurysmal formation. The authors have sufficiently presented all pathophysiological proposed pathways under investigation behind this paradox. Our aim was to highlight some important concepts with clinical significance.

It seems that there is sufficient data to support the theory of synergistic effect of multiple different aorta-protective mechanisms of DM, with clinical implications. In a case-control study [2], the overall pooled incidence rate of thoracic and abdominal aortic aneurysm was 15% lower in type 2 DM cohort than in non-DM cohort. Interestingly, patients with DM and aortic aneurysms were significantly less likely to present with rupture or to die from abdominal aortic aneurysm (AAA) rupture, when compared to non-diabetic ruptured aneurysm patients [3]. The same applies to aortic dissection, as found by a Swedish National Diabetes Register analysis, in which patients with type 2 DM had significantly reduced risks of aortic aneurysm and aortic dissection, compared with matched population-based control subjects [4].

To account for this inverse relationship between DM and aneurysmal formation, the investigators of the Reduction of Atherosclerosis for Continued Health trial, suggested that the constitution of the abdominal aortic wall was different in patients with DM compared to non-diabetic subjects [5]. Among the most important proposed mechanisms is the hyperglycemia-mediated aortic stiffening, which in turn results in reduced aortic wall stress. This is mainly attributed to a progressive increase in extracellular matrix (ECM) volume, mediated by decrease in ECM degradation and an increase in ECM synthesis, all driven by hyperglycemia [6]. Another major contributing factor is the role of matrix metalloproteinases (MMPs) [7]. The study by Patel et al. [1] reasonably highlighted that an increase in proteases like MMPs and a depression in their inhibitory enzymes (TIMP's) leads to the destruction of collagen and elastin in the ECM and loss of smooth muscle cells, which in turn leads to aneurysm formation. Interestingly, hyperglycemia has been associated with a reduced level of MMP expression and as a result, DM has been linked to lower potential for aneurysmal formation [8]. An additional pathway with clinical significance is the advanced glycation end-product formation by hyperglycemia and non-enzymatic cross-linking of ECM proteins [9]. Again, a common aftereffect

can be spotted; increase in vessel stiffness [10]. A further explanation of how the aorta is resistant to aneurysmal formation can be obtained by studying its relation to inflammatory process. Surprisingly, hyperglycemia has been found to reduce the expression of various pro-inflammatory cytokines [11]. Additionally, a very important and clinically significant factor is the role of oral hypoglycemic medications in reducing aneurysmal formation and growth. The mechanism behind this may be related to decrease in macrophage infiltration, MMP-9 and TNF- α levels [12] and is currently the subject of many multi-center studies.

Lastly, secondary hyperinsulinemia of DM has also been shown to decrease MMP expression, which is fundamental for thrombus renewal, and consequently protects the aneurysmal wall from rapid growth [13].

In conclusion, the study by Patel et al. [1] has nicely summarized that “these findings indicate a paradoxically beneficial effect of the otherwise highly detrimental diabetic state.” What is now left to be considered is how we incorporate this newly gained knowledge to pharmacologically target attenuation of aneurysm expansion and prevention of subsequent rupture for de novo and post-intervention aneurysms.

References

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