

J. Zsuga: Dimethylarginines at the crossroad of atherosclerosis and insulin resistance  
DEPARTMENT OF NEUROLOGY MEDICAL AND HEALTH SCIENCES CENTER  
UNIVERSITY OF DEBRECEN; DEBRECEN, 2007.

The link between the evolution of atherosclerosis and endothelium derived NO synthesized by endothelial NOS (eNOS) is long acknowledged since endothelial dysfunction (that is the deterioration of endothelium dependent NO release) is viewed as the forerunner of atherosclerosis. Additional to this a novel insulin sensitizing mechanism was described that is also linked to NO dependent mechanisms e.g. the activation of nNOS and is able to enhance the insulin sensitivity of striated muscle. There exists yet a third isoform of NOS, the inducible isoform (iNOS) that yields the highly reactive peroxynitrite. The different effect of these three distinct isoforms of NOS came into the focus of our attention due to the identification of a novel endogenous nitric oxide synthase inhibitor the asymmetrical dimethylarginine (ADMA). ADMA inhibits the three isoforms with different kinetics.

Within the frame of our research on one hand we investigated if the simultaneous inhibition of eNOS and nNOS is able to contribute to the evolution of atherosclerosis and insulin resistance. On the other hand we assessed if the inhibition of iNOS is able to confer beneficial effect in a condition when the enzyme is probably induced e.g. in early-onset atherosclerosis

We found that SDMA or rather the proportion of ADMA/SDMA (a more appropriate indication of the intracellular ADMA level) showed positive correlation with the HOMA index used for the characterization of insulin resistance, an effect that remained significant even after correction for confounders if only atherosclerotic patients were included in the analysis.

On the other hand, we found that ADMA level negatively correlated with intima-media thickness a surrogate for cerebro- and cardiovascular diseases, and this negative correlation remained significant even after correction for confounders.

**Summarizing:** *our results we propose that ADMA assumes a central role in the simultaneous evolution of atherosclerosis and insulin resistance, furthermore we found that near-normal ADMA level is beneficial in atherosclerotic patients, probably by inhibiting peroxynitrite formation.*