Diabetes mellitus as a factor enhancing aortic stenosis progression: new molecular mechanisms

Recent studies have provided a strong evidence that the pathomechanisms of atherosclerosis and aortic stenosis share several similarities such as the local inflammation with infiltration of macrophages and coagulation pathway activation as well as risk factors such as diabetes mellitus. Numerous reports on the molecular mechanism of atherogenesis indicate that formation of advanced glycation end products (AGEs) together with oxidative stress increase and chronic inflammation are involved in disease development, particularly in diabetic patients. Precisely, metabolic factors such as elevated free fatty acids, high glucose levels or AGEs induced reactive oxygen species in vascular cells leading to ongoing AGE formation and to gene induction of proinflammatory cytokines which have been specified as crucial step during atherosclerotic plaque formation. Unfortunately little is known about the association of diabetes, AGEs and aortic stenosis despite the strong impact of diabetes on coronary atherosclerosis.
Our rationale is that, similar to atherosclerosis, diabetes can lead to the glycation of valvular proteins, potentiate the inflammatory processes within stenotic valves involving coagulation cascade proteins and reactive oxygen species, which in turn can lead to the massive fibrosis and calcification.
On the basis of current knowledge and the preliminary data of our team, **the goal of planned experiments is multidirectional evaluation of molecular mechanisms underlying effects of hyperglycemia on inflammation and calcification within aortic valves in patients with aortic stenosis.**
We assume that the enhanced accumulation of AGEs due to hyperglycemia and increased expression of the receptor for AGEs (RAGE) in patients with aortic stenosis and concomitant diabetes might be responsible for accelerated valve calcification through activation of NFkB/MAP kinases pathways and glycation of valve scaffold proteins (collagen, elastin, laminin) and extracellular matrix proteins. Simultaneously, hyperglycemia leads to activation of valvular interstitial cells through AGEs/RAGEs, enhancing production of reactive oxygen species which in turn leads to faster valve fibro-calcification. Moreover enhanced *in loco* expression of tissue factor in patients with diabetes compared to those with isolated aortic stenosis may accelerate aortic valves degeneration.
The planned research project will investigate the effect of hyperglycemia and glycation on the biology of aortic valves, both at the cellular level (*in vitro* cultures) and tissue level (*in loco*). The proposed research objectives will be implemented multidirectionally, with the modern methods including Raman microscopy, flow cytometry, immunofluorescence, or Real time PCR.
Experiments will be performed in blood obtained from150 patients with aortic stenosis with or without diabetes. The valve interstitial cells will be isolated from aortic valves obtained from patients undergoing aortic valve replacement and will be maintained in *in vitro* culture.

Verification of presented hypotheses might allow to gain a new knowledge about the inter-correlations between glycemic disorders, inflammation and procoagulatory state and aortic valve calcification.
New data that will be collected during the current project might give the opportunity for the implementation of novel therapeutic strategies potentially limiting or inhibiting aortic stenosis development.