

25. Left ventricular pressure-volume measurements and myocardial gene expression profile in type-2 diabetic Goto-Kakizaki rats

Alice Lehner
Dr. Sevil Korkmaz-Icöz
Dr. Shiliang Li
Adrian Vater
Dr. Tamás Radovits
Mihály Ruppert
Paige Brlecic
Dr. Markus Zorn
Prof. Matthias Karck
Prof. Gábor Szabó

Background The Goto-Kakizaki (GK) rat, a non-obese model of type-2 diabetes mellitus (DM), was generated by the selective inbreeding of glucose intolerant Wistar rats. This is a convenient model for studying diabetes-induced cardiomyopathy independently from the effects of the metabolic syndrome. We investigated the myocardial functional and structural changes, and underlying molecular pathomechanisms of short-term and mild type-2 DM.

Methods We evaluated both mechanical and electrical aspects of cardiac function. Additionally, heart sections were inspected for histopathology by hematoxylin and eosin or Masson's trichrome staining, and using RT2 Profiler™ PCR Arrays, we determined the expression patterns of 125 genes.

Results The presence of DM was confirmed by the impaired oral glucose tolerance in the GK rats compared to the age-matched nondiabetic Wistar rats. In GK rats, although the systolic indexes were not altered, left ventricular diastolic stiffness was increased in comparison with nondiabetics (end-diastolic pressure-volume relationship: 0.12 ± 0.04 vs 0.05 ± 0.01 mmHg/ μ l, $p < 0.05$). Additionally, DM was associated with cardiomyocyte hypertrophy and histological evidence of increased myocardial fibrosis. Plasma pro-B-type natriuretic peptide, high-sensitive cardiac troponin-T, glucose (12.4 ± 1.8 vs. 8.3 ± 0.6 , $p < 0.05$), urinary glucose, and serum insulin (1.71 ± 0.45 vs 0.76 ± 0.09 μ g/l, $p < 0.05$) concentrations were significantly higher in GK rats compared to the controls. Among the 125 genes surveyed, DM significantly altered the myocardial expression of 5 genes (upregulation of natriuretic peptide precursor-A and connective tissue growth factor, downregulation of C-reactive protein, interleukin-1 β , and tumor necrosis factor mRNA-level). The ECG recordings revealed no significant differences. Compared to the control group, diabetes had no effect on cardiomyocyte DNA strand breakage, as reflected by the quantitative assessment of TUNEL-positive cell nuclei.

Conclusions In the early stage of DM, we observed a downregulation of inflammatory markers in the diabetic heart tissue. Further assessments are required to reveal if they play a role in the early stage of diabetic cardiomyopathy development.