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Oral treatment with zinc complex of acetylsalicylic acid prevents diabetic cardiomyopathy in a rat model of type 2 diabetes

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Type 2 diabetic patients are at increased risk of cardiomyopathy and heart failure is a major cause of death for these patients. Growing evidence indicates that proinflammatory cytokines can cause sustained development of insulin resistance and anti-inflammatory medications may reverse the process of it. The aim of this study was to investigate the effects of oral administration of zinc and acetylsalicylic acid (a traditional non-steroidal anti-inflammatory drug) in the form of bis(aspirinato)zinc(II) complex on different aspects of cardiac damage in Zucker diabetic rat (ZDF), an experimental model of type 2 diabetic cardiomyopathy.

Nondiabetic control and diabetic ZDF rats were pretreated orally with either zinc complex of acetylsalicylic acid ($Zn(ASA)_2$) or vehicle for 24 days. Experiments were performed at the age of 30-32 weeks. Both electrical activity and left-ventricular structural/functional parameters were assessed *in vivo* via electrocardiogram and Millar pressure-volume conductance catheter system, respectively. Myocardial histological analysis was performed.

$Zn(ASA)_2$ treatment decreased blood glucose concentration (39.6±3.1 mM vs. 50.4±2.6 mM, $p<0.05$), normalized significantly impaired left-ventricular contractility index (E_{max}: 3.7±0.4 mmHg/µl vs. 1.9±0.6 mmHg/µl, $p<0.05$), passive left-ventricular stiffness (end-diastolic pressure-volume pressure-volume relationship, EDPVR: 0.064±0.008 mmHg/µl vs. 0.084±0.014 mmHg/µl), and diastolic dysfunction (left-ventricular end-diastolic pressure, LVEDP: 6.5±0.6 mmHg vs. 7.9±0.7 mmHg). Furthermore, ECG revealed a restoration of elevated ST-segment (0.03±0.02 mV vs. 0.09±0.01 mV, $p<0.05$) and prolonged corrected QT-interval (63±3 ms vs. 83±4 ms, $p<0.05$) by $Zn(ASA)_2$. Histological examination revealed an increased in cardiomyocytes transverse cross section area in the hematoxylin and eosin stained sections in diabetic rats compared to controls which was significantly decreased after treatment with $Zn(ASA)_2$. Furthermore, histological analysis of myocardial tissue using acid

fuchsin orange G-stain revealed a significant increase in fibrotic formation observed in diabetic rats when compared with controls and $Zn(ASA)_2$ administration showed similar collagen content in ZDF+$Zn(ASA)_2$ rats compared to nondiabetics. Significant increase in density of TUNEL-positive cell nuclei in the myocardium of diabetic rats, indicating DNA-fragmentation was significantly decreased by $Zn(ASA)_2$. In addition, treatment with $Zn(ASA)_2$ significantly decreased nitrotyrosine formation in the myocardium of diabetic animals.

We demonstrated that oral treatments of diabetic rats with $Zn(ASA)_2$ significantly decreased blood glucose levels and prevented diabetic cardiomyopathy based on electrical and mechanical changes, and histological evaluation. Furthermore, $Zn(ASA)_2$ reduced nitro-oxidative stress and reduced DNA fragmentation. Oral administration $Zn(ASA)_2$ may have therapeutic potential with the aim of preventing cardiac complications in type 2 diabetic patients.