**PDE5 INHIBITION WITH SILDENAFIL ATTENUATES ALCOHOL-INDUCED CARDIAC DYSFUNCTION IN OBESE DIABETIC MICE: ROLE OF MicroRNA 21**

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**Objective:** Excessive intake of alcohol under diabetic condition leads to increased stress and causes both transient and lasting structural changes including fibrosis in heart. We tested the hypothesis whether phosphodiesterase5 (PDE5) inhibitor, sildenafil prevents alcohol-induced cardiac dysfunction in Type 2 Diabetes Mellitus (T2DM) db/db mice. Also, considering the role of microRNA-21 (miR-21) in fibrosis through regulation of ERK1/2-MAP kinase signaling and inhibition of sprouty-1 (Spry-1), we also examined this pathway in alcohol-induced cardiac dysfunction in obese diabetic mice.

**Methods:**Adult male db/db mice were randomized to receive: saline as control (0.2 ml; i.p, n =5) or alcohol (1.5 g/ BID; i.p, n=5) or alcohol with sildenafil (0.7mg/kg/day; i.p, n=5) for 3 days.

**Results:** Echocardiography showed a decline in Ejection Fraction (EF) in mice treated with alcohol as compared to their baseline (P < 0.05). Treatment with sildenafil in combination with alcohol showed normal EF. Moreover alcohol treatment increased PDE5 protein expression. Real time PCR using TaqMan microRNA probe showed 1.5 fold increase in miR-21 level in the heart after alcohol treatment. Protein analysis showed downregulation of spry-1 (target of miR-21) and up regulation of ERK1/2 phosphorylation (inhibited by spry-1). Sildenafil treatment prevented the upregulation of miR-21 and hence increased the level of spry-1 and a concomitant decrease in ERK1/2 phosphorylation.

**Conclusion:**Alcohol-induced upregulation of miR-21 in db/db mice with subsequent decrease in spry-1 and an increase in Phosphorylation of ERK1/2 suggest the role of this signaling cascade in fibrosis and cardiac dysfunction. Therapeutic intervention using sildenafil prevented LV dysfunction caused by alcohol intake and fibrosis signaling pathway.