**MANAGEMENT OF METABOLIC SYNDROME AND ATHEROSCLEROSIS IN MULTIPLE MOUSE MODELS OF HUMAN TYPE II DIABETES AND HEART DISEASE**

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**Background**- Metabolic syndrome is defined by increased levels of LDL cholesterol and triglycerides and decreased levels of HDL cholesterol. We have examined whether inhibition of glycosphingolipid synthesis can manage metabolic syndrome in a mouse model of type-II diabetes, and reduce aortic intima-media thickening, body weight and blood glucose levels.

**Methods and Results**- Type II diabetic mice (db/db) and normal mice (C57/BL6) (12 weeks of age, n=6 per group) were fed regular chow for 30 weeks. The diabetic mice were fed:a. vehicle (5% Tween-80 in PBS; 100uL) daily for 6 weeks (placebo group)and b. 5mg/kg body weight of biopolymer-encapsulated; D-threo-1-phenyl-2-decanoylamino-3-morpholino-1-propanol (BPD), an inhibitor of glycosphingolipid(GSL) synthesis daily, by oral gavage. At 36 weeks of age, echocardiography was performed to measure aortic intima–media thickening (Ao-IMT). Increased Ao-IMT was observedin *db*/*db* mice, compared to normal mice. However, BPD treatment reversed Ao-IMT thickening in *db*/*db* mice, accompanied by decreased levels of GSL, LDL cholesterol, triglycerides, and glucose. However, treatment significantly raised HDL cholesterol, in db/db mice. BPD decreased cholesterol level by increasing the expression of multiple genes e.g. HMG-Co-A reductase, LDLr, SREBP2, cholesterol efflux genes, e.g., ABCG5/ABCG8, LXR, genes expressing scavenger protein’s CD36, bile acids Cy7- α hydroxylase, and FXR. Triglycerides were decreased due to an increase in the expression of genes for lipoprotein lipase, VLDLr, and PPAR-α. Our mechanistic studies showed that decreased cholesterol levels correlated with decreased NPC1 gene/protein expression and mammalian target of rapamycin (mTOR-C1); and a reduction in body weight.

**Conclusions**- Inhibition of glycosphingolipid synthesis helped manage metabolic syndrome, reduce body weight, glucose levels, and aortic intima-media thickening in type II diabetic mice by way of reducing cholesterol sensing protein NPC-1 and mTOR-C-1.