ABSTRACT

Background: Sugar rich diet induces inflammation and insulin resistance (IR) mainly through gut microbiota alteration. Gut microflora dysbiosis increases lipopolysaccharide (LPS) and reduces the short chain fatty acids (SCFAs) levels to impair the insulin signaling cascades by different molecular pathways, which progresses into IR. This study was designed to investigate the effect of spectrum specific antibiotics and chitosan administration on gut microflora mediated signaling pathways to prevent the diet induced diabetes.

Methods: Healthy male wistar rats were divided into non-diabetic group with a normal diet (CD), diabetic group with high sucrose diet (HSD) and three antibiotics and chitosan administrated groups along with HSD. The effect of their administration was studied at physiological, biochemical, inflammatory and molecular levels. Further, effect of altering the target specific microbial population was studied in context with insulin sensitivity.

Results and Conclusion: After 12 weeks of the study, significant alterations in three major gut dominant microbial phyla i.e Firmicutes, Bacteroides and Proteobacteria along with four genera i.e. *Lactobacilli*, *Bifidobacteria*, *Escherichia* and *Clostridia* were observed in all the experimental groups. Cefdinir administration in HSD had significantly reduced the fasting glucose, serum triglycerides and cholesterol levels compared to HSD control. It had reduced the metabolic endotoxemia by decreasing the population of Gram negative phyla, i.e. Bacteroidetes and Proteobacteria in the gut. Reduced endotoxin levels had decreased the mRNA expression of TLR4 and NLR1, which further downregulated the NF-κB activity to decrease the expression of proinflammatory cytokines. Chitosan administration in HSD had increased the population of *Lactobacilli* and *Bifidobacteria* with a decrease in *Escherichia* proving its prebiotic properties. Cefdinir and chitosan receiving animals had shown significant increase in the major SCFAs, such as butyrate and propionate level, while decrease in acetate as compared to HSD control. They had increased the mRNA expression of GPR43 and GLUT4 in colonic tissue after 12 weeks of the administration. These observations suggest that Gram negative spectrum antibiotic, i.e. cefdinir and prebiotic, i.e. chitosan administration in HSD can prevent the progression of IR through gut microbiota alteration, reducing endotoxin

and microbes mediated inflammation. The EL and ES coated linezolid as well as cefdinir microspheres had successfully formulated using solvent evaporation method for their targeted delivery to proximal small intestine and colon respectively. The enteric coated antibiotics microspheres had shown smooth and spherical surface morphology with a particle size in range of 10-30 µM. The ES and EL coated antibiotics microspheres were administrated orally along with an HSD in wistar rats for 12 weeks of the period. At the end of the study, ES and EL coated antibiotics microspheres had shown divergent effect on the physiological, biochemical and inflammatory parameters. ES cefdinir microspheres had efficiently shown to decrease the inflammation through their specific target to the colonic microbiota. ES cefdinir microspheres had significantly increased the insulin sensitivity compared with EL cefdinir through modulating the microbiota mediated inflammation and metabolites profiling. These results suggest that colonic microbiota play an important role in the progression of diet induced diabetes through the alteration of metabolites. Thus, selective manipulation of the colonic microbiota can be an emerging therapeutic strategy for the prevention of IR.