Abstract

Dysfunctional adipocytes and β-cells are crucial in advancing obesity-induced Type 2 Diabetes (T2D). Adipocytes produce many biomolecules, known as adipokines, anti-inflammatory (omentin-1 and vaspin) and pro-inflammatory (resistin). In the present study, the association between *resistin*, *omentin-1* and *vaspin* genes polymorphisms, their transcript and protein levels, and genotype-phenotype correlation with metabolic parameters and T2D susceptibility were explored in Gujarat population. *Resistin* rs1862513 C/G polymorphism is strongly associated with elevated resistin protein levels and increased BMI, FBG and TC levels. *Omentin-1* genetic variants are not associated with T2D, but reduced omentin-1 protein levels are associated with T2D. *Vaspin* rs2274907 A/T polymorphism is strongly associated with its reduced transcript and protein levels. These metabolic alterations may play a role in the development of T2D. A neurotransmitter, γ-aminobutyric acid (GABA) is secreted by β-cells, which exerts autocrine protective and regenerative effects. However, at the metabolic level, calorie restriction (CR) improves insulin sensitivity and fasting blood glucose (FBG) levels. We have developed high-fat diet and streptozotocin-induced (HFD+STZ) T2D mouse model and studied the effect of CR, GABA, and combination of CR and GABA. GABA monotherapy showed reduced FBG levels, improved insulin sensitivity and glucose tolerance, increased insulin and c-peptide levels, and decreased gluconeogenesis and glycogenolysis compared to the HFD+STZ group. The GABA treated group also showed significant increase in β-cell proliferation and neogenesis with significantly reduced β-cell apoptosis compared to the HFD+STZ group. CR diet-fed mice showed reduced body weight and triglycerides levels, along with improved insulin sensitivity, reduced gluconeogenesis and glycogenolysis compared to the HFD+STZ group. CR group also showed elevated expression of mitochondrial biogenesis markers and oxygen consumption rate by ETC complexes I-III compared to the HFD+STZ group. CR group showed no β-cell regeneration and no improvement in β-cell apoptosis compared to the HFD+STZ group. GABA+CR treated group showed improved glucose homeostasis by increasing insulin sensitivity and glucose tolerance, enhancing the transcript levels of key markers of glucoregulatory enzymes and lipid metabolism, and increasing mitochondrial biogenesis and ETC complex activities compared to HFD+STZ group. Further, the combination therapy showed significant increase in β-cell regeneration and reduced β-cell apoptosis compared to HFD+STZ group.

Keywords: Lipids, Obesity, Single Nucleotide Polymorphism, Linkage Disequilibrium, Haplotype, Genotype-Phenotype correlation; Pancreas; β-cell apoptosis; β-cell regeneration; Islet neogenesis; Regenerative medicine.