Abstract

Diabetes mellitus is a public health concern of the twenty-first century. Obesity, dyslipidemia and insulin resistance co-exist with a significant β-cell loss in type 2 diabetes (T2D). Adipocyte hyperplasia and hypertrophy in obesity leads to increased levels of pro-inflammatory adipokines, and decreased levels of anti-inflammatory adipokines such as Adiponectin (ADIPOQ). Adiponectin plays a key role in maintaining energy homeostasis and insulin sensitivity and its reduced levels have been reported in obesity and T2D. As T2D is chronic in nature with altered metabolic pathways, the use of complementary medicine to control T2D, by reducing insulin resistance and increasing β-cell regeneration simultaneously might provide a promise to ameliorate T2D. The present study evaluated the association between *ADIPOQ* gene polymorphisms, -11377C/G (rs266729) in promoter, +10211T/G (rs17846866) in intron 1, +45T/G (rs2241766) in exon 2 and +276G/T (rs1501299) in intron 2; plasma high molecular weight (HMW) and total adiponectin levels; and genotype-phenotype correlation with metabolic parameters and T2D susceptibility. The study also aimed to understand the ameliorative potential of pitavastatin and L-glutamine in combination in high fat diet (HFD) and streptozotocin (STZ) induced T2D mouse model. +10211T/G and +276G/T was found to be associated with risk towards T2D, reduced HMW adiponectin/ total adiponectin ratio, and increased fasting blood glucose (FBG), body mass index (BMI), triglycerides (TG), total cholesterol (TC). Further, we saw an increased GGTG haplotype in obese patients of Gujarat population. The combination treatment could significantly reverse insulin resistance and glucose intolerance as indicated by increased pAkt/Akt ratio, IR1β and AdipoR1 protein levels in skeletal muscle and a significant correction in the enzyme activities of hepatic gluco-regulatory pathway. There was also a significant reduction in FBG, TG, TC, low-density lipoprotein, and increased insulin levels and normo-adiponectinemia, increased mitochondrial I, II and III complex activities, and mitochondrial biogenesis in addition to an increased β-cell proliferation and reduced β-cell death in the combination group. However, the monotherapies showed a marginally significant enhancement in the above parameters. Thus, we conclude that *ADIPOQ* +10211T/G and +276G/T polymorphisms and GGTG haplotype confers genetic susceptibility towards T2D in Gujarat population, and the combination of pitavastatin and L-glutamine ameliorates T2D by improving glucose homeostasis, lipid profile, mitochondrial biogenesis and β-cell survival.