4. Conclusions

Type 2 diabetes (T2D) has a stronger link to family history and lineage than type 1 diabetes (T1D). Studies on identical twins have shown that genetics play a vital role in the development of T2D. However, it also depends on environmental factors such as lifestyle. Obesity has a tendency of running in families and ethnicities. When one has a family history of T2D, it may be difficult to figure out whether T2D is due to the lifestyle factors or genetics but most often it is due to both. Though, we cannot choose our genes, we still do get the option of choosing our lifestyle. Also, T2D shows significant reduction in β-cell mass apart from insulin resistance, hyperglycemia, hyperlipidemia, mitochondrial dysfunction, etc. While the existing treatment approaches focus more on managing the glycemic levels and T2D associated comorbidities, the β-cell regeneration is getting more attention.

Our population-based study showed that *ADIPOQ* +10211T/G and +276G/T polymorphisms were significantly associated with T2D in Gujarat population, while the GGTG haplotype showed increased risk towards developing obesity-induced T2D. The +10211T/G and +276G/T polymorphisms were significantly associated with increased fasting blood glucose (FBG) levels, dyslipidemia and reduced HMW: total adiponectin ratio. (Figure 4.1)

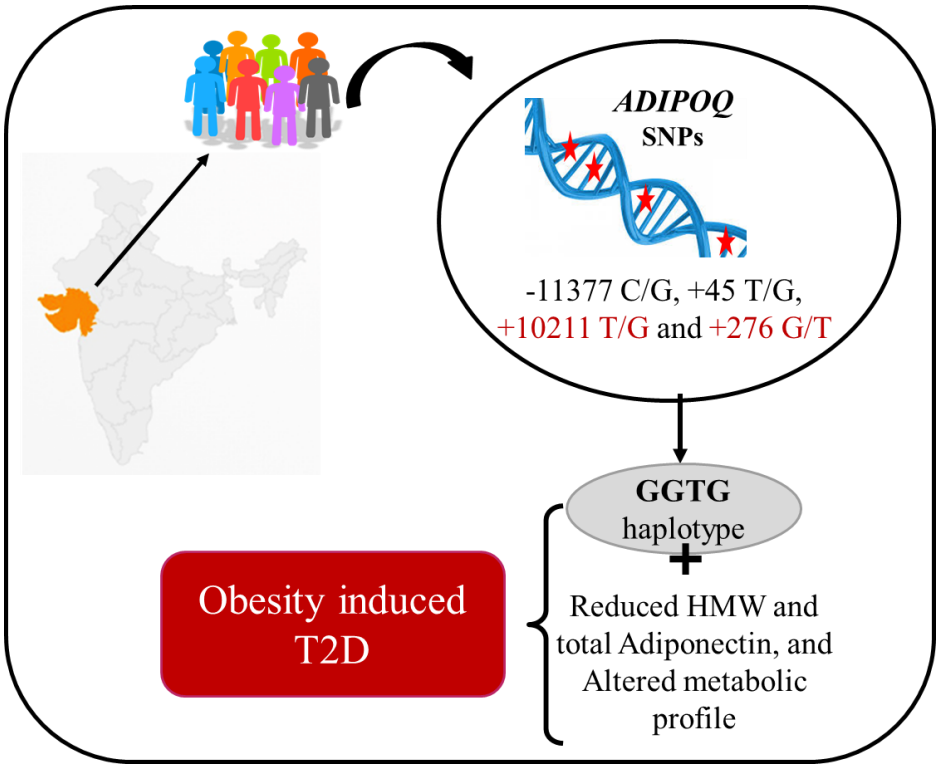

Figure 4.1: Our population study suggests association of *ADIPOQ* +10211 T/G and +276 G/T with reduced plasma HMW: total adiponectin ratio, increased FBG and dyslipidemia. In

addition, the haplotype GGTG (-11377 C/G, +45 T/G, +10211 T/G and +276 G/T) conferred risk towards the development of obesity-induced T2D.

We have further demonstrated the ameliorative potential of pitavastatin in combination with L-glutamine in T2D mouse model. Pitavastatin is a lipid lowering drug that acts by inhibiting HMG-CoA reductase and L-glutamine is a potentiator of GLP-1. We have shown that the two molecules could bring about normoadiponectinemia, increased IR1β, pAkt/Akt and AdipoR1 levels, and improve glucose homeostasis in terms of increased glucose tolerance and reduced insulin resistance. Further, the combination therapy showed significant improvement in the lipid profile, mitochondrial biogenesis, mitochondrial ETC complex I, II and III oxygen consumption rates, and also induce β-cell regeneration via proliferation (Figure 4.2).

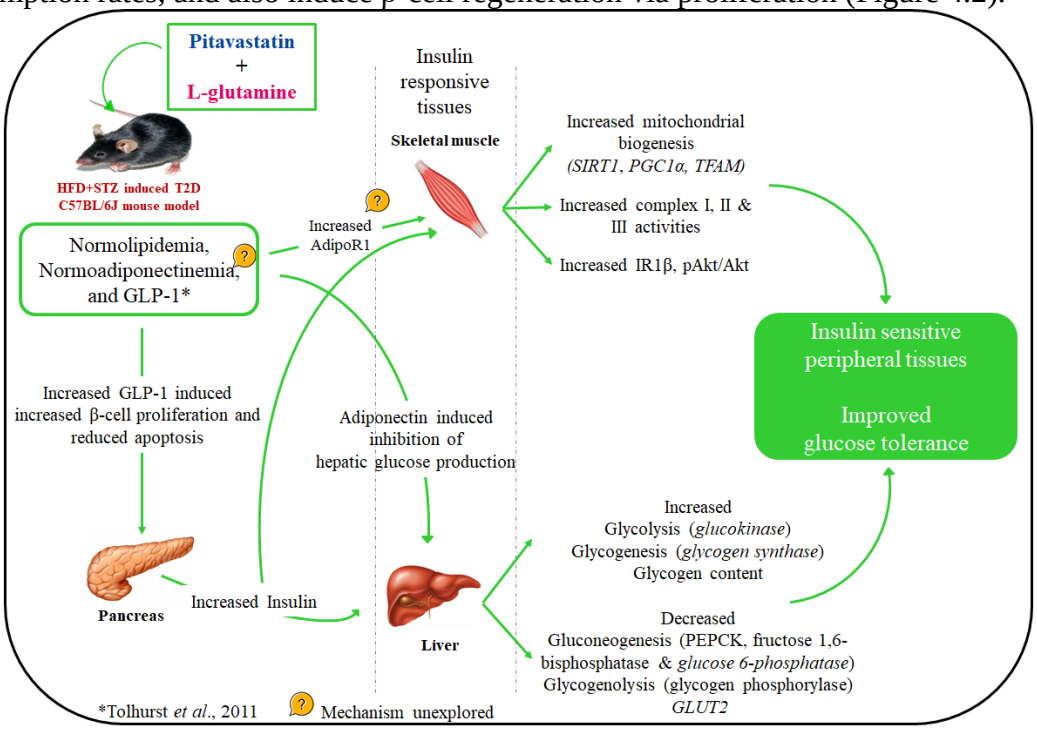

Figure 4.2: Effect of combination therapy on amelioration of T2D manifestations: The combination therapy could bring about normoadiponectinemia (mechanism unexplored in this study) and reduce TG, TC and LDL. L-glutamine is known to increase GLP-1 (Tolhurst *et* al., 2011) which induced β-cell proliferation and reduce β-cell apoptosis. The increased β-cell mass led to increased insulin synthesis. Insulin and adiponectin together inhibited PEPCK and fructose 1,6-bisphosphatase activities, and *glucose 6-phosphatase and GLUT2* transcript levels while increasing *glucokinase* and *glycogen synthase* transcript levels, and glycogen content in liver. The increased insulin further increased mitochondrial ETC complex I, II and III activities and *SIRT1, PGC1α* and *TFAM* transcript levels in skeletal

muscle. Also, the levels of AdipoR1 in skeletal muscle was increased in combination therapy (mechanism unexplored in this study) leading to activation of insulin signalling pathway via IR1β and phosphorylation of Akt. Overall, the drugs could work together to bring about normolipidemia, reverse mitochondrial dysfunction, decrease gluconeogenesis, glycogenolysis, glycogen synthesis and *GLUT2* expression. The combination therapy could also reduce β-cell death, enhance glucose tolerance and insulin sensitivity thus ameliorating T2D manifestations in HFD+STZ mouse model.

Reference

Tolhurst, G., Zheng, Y., Parker, H. E., *et al.* (2011). Glutamine triggers and potentiates glucagon-like peptide-1 secretion by raising cytosolic Ca2+ and cAMP. Endocrinology, 152(2), 405-413.