Summary & Conclusion
SUMMARY AND CONCLUSION

Diabetes is an alarming disorder of the third world. The rapidly increasing prevalence of T2D is becoming a tremendous public health problem that affects more than 170 million people worldwide. Currently, India is the diabetic capital of the world. T2D is a complex metabolic disorder with two major pathophysiological features: insulin resistance and pancreatic β-cell dysfunction. The mechanism of this disease remains unknown, however, environmental factors and genetic variations are considered two major contributors as well as the interaction between these factors, determine the phenotype to onset and development of T2D.

Diabetes mellitus is generally categorized as type 1 (insulin-dependent diabetes dependent diabetes or Juvenile-onset diabetes), type 2 (non-insulin dependent or adult-onset diabetes and gestational diabetes. As the pathophysiology of different types of diabetes varies, interventions for treating them should also be specific to its type. This essentiates the need for correct categorization of diabetes. The objectives of the study were to identify suitable methods and biochemical markers for the identification, confirmation of genes and associated single nucleotide polymorphisms with T2D, to analyse the anthropometric and biochemical parameters to study the association with T2D and with other metabolic disturbances.

Subjects who participated in the study carried out during July 2009 to December 2011 were screened for type 2 diabetes by analysing fasting and post prandial glucose levels. Participants found to be diabetic were further selected for the study based on selected inclusion criteria namely, age above 30 and below 65 years, symptoms like polyuria, polydipsia and unintentional weight loss, baseline random blood-glucose > 200mg/dl and glycosylated hemoglobin > 7.0%.

The study was carried out with 341 nondiabetic controls and 346 type 2 diabetic cases. The general profiles of these subjects were recorded to analyse the impact of age, sex, family history of diabetes and lifestyle pattern on the types 2 diabetes. Anthropometric measurements namely height, weight, body-fat percentage, BMR and BMI and blood pressure were recorded to study the relationship between
blood pressure, obesity and type 2 diabetes. All the diabetic patients of the study were
categorized as normal weight and overweight along with lifestyle modification.

Biochemical analysis namely fasting blood glucose, postprandial blood
glucose, glycated hemoglobin (HbA1c), lipid parameters (total cholesterol,
triglycerides, HDL-C and LDL-C), total protein, urea, creatinine, CRP and activities
of selected liver enzymes namely, serum glutamic oxaloacetic transaminase (SGOT)
and serum glutamic pyruvic transaminase (SGPT) was carried out. Metabolic
hormone namely, TNFα, IL-6, C-Peptide, insulin and leptin; adipokines like
adiponectin and resistin were also carried out at diagnosis.

Salient findings of the study

- This investigation showed that Mysore district population is at considerable
  risk of type 2 diabetes and have one of the highest prevalence rates of type 2
diabetes. Results from this investigation also confirm that among this group,
type 2 diabetes occurs at a much younger age and at lower body mass index
than in other ethnic groups.
- The increased waist to hip ratio and thereby increase in abdominal obesity was
  seen in a greater percentage in type 2 diabetic patients compared to normal
  subjects. This may be due to the greater percentage of type 2 diabetic patients
  adopting a sedentary lifestyle. Family history of diabetes was found to be
  closely associated in patients with type 2 diabetes.
- Sedentary lifestyle was found to be more pronounced in type 2 diabetics than
  controls. The mean BMI of type 2 diabetic patients were found to be more
  compared to non diabetic controls.
- Blood pressure was found to be increased in type 2 diabetics indicating a
  relationship between blood pressure, obesity and type 2 diabetes.
- A significant increase was observed between fasting, postprandial blood
  glucose and HbA1c levels in types 2 diabetics than controls. Cholesterol,
  triglyceride and LDL levels were observed significantly high in type 2 diabetic
  patients compared to non diabetic controls. There was a significant difference
  observed in blood urea nitrogen, creatinine, protein levels and also significant
difference was observed in the activities of liver enzymes namely, serum
  glutamic oxaloacetic transaminase and serum glutamic pyruvic transaminase.
However, there was no significant difference between HDL levels between the two groups. The levels of CRP were found to be increased in diabetic patients indicating the risk of CVD. Incidence of CVD among the diabetics in the present study was found to be associated with each of the lipid parameters namely total cholesterol, triglyceride, HDL cholesterol, LDL cholesterol.

- The results of this study also reveal a high prevalence of hypercholesterolemia, hypertriglyceridemia, high LDL-C, and low HDL-C levels, which are well-known risk factors for CVD. Insulin affects apolipoprotein production in the liver and regulates enzymatic activity of lipoprotein lipase (LpL) and cholesterol ester transport protein. All the above factors are responsible for dyslipidemia in T2D. Insulin deficiency reduces the activity of hepatic lipase and therefore, several steps involved in the production of biologically active LpL might be altered in T2D.

- The increase in C-peptide levels of type 2 diabetic patients in the present study, suggests that insulin resistance and not destruction of β-cells is the mechanism of occurrence of type 2 diabetes.

- The decrease in the total level of TNFα and IL6 in the present study, indicate circulating concentrations of these pro-inflammatory cytokines are relatively low, and their main effects on insulin resistance and lipid metabolism are mediated locally in a paracrine manner.

- The equal resistin level between two groups is in agreement with the fact that, the expression levels of resistin in human adipocytes are very low and there is no apparent increase in expression of resistin in human obese insulin resistant states leaving the role of resistin uncertain.

- The increase in HOMA-IR levels in diabetic subjects suggests a direct relation between insulin resistance and the degree of variability present in both health and disease.

- The decrease in adiponectin concentration of the diabetic subjects appears to be a contributing factor in the development of insulin resistance in obesity and type 2 diabetes.

- The increased leptin level in diabetic subjects is may be due to, leptin act on skeletal muscle to improve insulin action possibly via activation of AMPK and increased fatty acid oxidation suggesting that it probably does not play a significant role in insulin resistance.
It is found that elevated plasma levels of several biochemical parameters, and inflammatory markers were independent predictors of T2D. The findings for this study support the hypothesis that low-grade systemic inflammation is an underlying factor in the pathogenesis of T2D. The data from this particular study also provide further evidence that inflammatory markers might provide a method for early detection of CVD risk. These data might have significant implications for the prevention and treatment of T2D.

**DNA Study**

- Common variants in SNP rs563694 in G6PC2 locus were significantly associated with type 2 diabetes.
- Common variant in rs4402960 of IGF2BP2 gene was associated with type 2 diabetes.
- The SNP rs10811661 variant in CDKN2A/B gene was found to be associated with type 2 diabetes.
- The SNP rs757210 in TCF2 gene is found to be associated with type 2 diabetes.
- The SNP rs7903146 in TCF7L2 gene, one of the most replicated common variant in type 2 diabetes, was found to be strongly associated with type 2 diabetes.
- The strong association of SNP rs7903146 (TCF7L2) with HOMA-IR, fasting and Postprandial glucose and HbA1c confirming the physiological role of TCF7L2 in glucose homeostasis.
- The SNP rs2166706 near MTNR1B shows association with increased risk of type 2 diabetes among South Indian populations.
- The genotype-phenotype analysis the SNP rs3847554 near MTNR1B shows association with increased fasting and post prandial glucose.
- The genotype-phenotype analysis for our study revealed the association of rs12779790 of CDC123-CAMK1D gene locus with cholesterol and triglycerides.
- The genotype-phenotype analysis for our study revealed the association of rs1111875 in HHEX gene with HDL and LDL and cholesterol.
- The other SNP’s (rs560887, rs780094, rs1402837, rs1260326, rs1801282, rs10946398, rs1799884, rs730497, rs13266634, rs10830962, rs10830963 and rs1387153) are not associated with type 2 diabetes or related biochemical and clinical parameters.
Conclusions from the present study

The best approach to prevent T2D in patients is early recognition of risk factors and aggressive therapy. Modification of lifestyle habits and management of systemic inflammation should be the major targets for prevention and treatment in T2D. Pharmacological therapies with anti-inflammatory properties might also play an essential role in T2D. Healthy diet, regular exercise, yoga and meditation, may also help in both reduction and prevention of T2D complications.

The present work has resulted in the identification of genes and their SNPs for type 2 diabetes and for the first time has provided an evidence to clearly suggest that, these genes may play a role in pathogenesis of T2D. In this study, we found that SNPs in nine genes are significantly associated with T2D. Our results emphasize the value of investigating the combined effect of several T2D associated polymorphisms. Indeed, even though many studies have shown that the genetic load has a measurable impact on T2D risk, our findings suggest that it could have an important role in determining clinical and pathophysiological phenotypes in diabetic patients.

Genetics of type 2 diabetes is a continuously evolving field. Most recent papers have identified novel additional loci associated to T2D, for most of the T2D risk loci, biological function and role in the disease are still unknown. Many further studies will be necessary to elucidate the role of genetics in this disease. Case-control studies with other genes also provided further insight into the genetics of type 2 diabetes in South Indian population.

Our findings support the conclusion that, in order to define metabolic phenotypes and perhaps personalized treatment and prognosis of T2D, genotyping might be a simpler and cheaper approach than using the gold standard techniques of clinical physiology.