SUMMARY

Diabetes is a dreadful affliction, not very frequent among men, being a melting down of the flesh and limbs into urine. The patients never stop making water and the flow is incessant…. Life is short, unpleasant and painful.

Artaeus of Cappadoica

Diabetes is a global disease with a huge adverse impact on health and mortality, particularly from cardiovascular disorders. It occurs at any time of life from infancy to old age. Type 2 diabetes mellitus is primarily a lifestyle disorder, which accounts for around 90% of diabetes cases and increasing at an astonishing rate particularly in developing countries like India. In 1995, it has been estimated that around 135 million people had this condition and this may increase to as many as 300 million by the year 2025.

Type 2 diabetes mellitus is a metabolic disease associated with a constellation of abnormalities including dyslipidemia, elevated plasma inflammatory markers and hypertension. This cluster of abnormalities often leads to the development of extensive arteriosclerosis in patients with type 2 diabetes mellitus and results in high rates of cardiovascular and cerebral vascular diseases, renal failure and blindness.

These complications not only significantly increase the morbidity and mortality rate and severely reduce the quality of life, but also pose a remarkable therapeutic challenge that is not addressed effectively by traditional therapies.

The present study was devoted to identify the immune mechanisms underlying these abnormalities and to assess the role of thiazolidinediones as an effective therapeutic strategy targeting the root cause, so as to maintain normal energy homeostasis and to prevent or delay the development of diabetic complications.
Most commonly employed oral hypoglycemic agents are sulphonylureas and biguanides. These drugs, however have disadvantages such as primary and secondary failure of efficacy as well as the potential for induction of severe hypoglycemia.

Drugs capable of reversing the insulin resistance and the potential to reduce long-term complications of type 2 diabetes are of current interest. Glitazones are those classes of drugs which were approved by the FDA for the treatment of type 2 diabetes mellitus. These agents share a common classical structure, namely thiazolidine-2-4-dione (TZD).

Thiazolidinediones are frequently used to improve insulin sensitivity in subjects with type 2 diabetes mellitus which is often accomplished by the development of excess adipose tissue and other complications.

This paradox may be explained by the following mechanisms. First, PPAR-γ agonists increase the number of small adipocytes that are more sensitive to insulin and having a less lipolytic nature. Second, thiazolidinediones act on adipose tissue to decrease not only the circulating free fatty acids (FFA) but also adipokines such as tumour necrosis factor α. Furthermore, TZD promote the secretion of adiponectin which has a favorable effect on insulin sensitivity.

Third, thiazolidinediones redistribute the body fat from the intra-abdominal region to the subcutaneous region. Moreover, it promotes the mobilization of ectopic fat accumulation of triglycerides in muscle and liver to adipose tissues. Finally, Thiazolidinediones modulate the inflammatory responses and possibly attenuate the complications of diabetes that cause significant morbidity and mortality.

The present study found some important differences between the two commonly used thiazolidinediones namely pioglitazone and rosiglitazone for the treatment of type 2 diabetes. Firstly, patients who were prescribed pioglitazone
had significantly greater improvements in blood lipid levels than patients who were prescribed rosiglitazone.

Currently available data clearly demonstrates more favorable effects of pioglitazone on plasma lipids and lipoproteins compared with rosiglitazone (lowering triglycerides and raising HDL to a greater extent). These differences may be associated with long term vasculoprotective advantages.

Secondly, improvements in HbA1c were statistically equivalent in both treatment groups. Both pioglitazone and rosiglitazone have been shown to decrease hepatic enzyme levels as tighter blood glucose levels are achieved. It would be speculated that the cardiac risk reduction would be more likely with pioglitazone than rosiglitazone. This would be derived from improved glucose control alone and might be partially offset by detrimental changes in some lipid levels.

From the present study Thiazolidinediones were found to improve the immune status in type 2 diabetic patients. It was also observed that pioglitazone was responsible for greater reduction in the levels of inflammatory markers contributing to restoration of normal immune system when compared to rosiglitazone. Thus pioglitazone was found to be more efficient with regard to the effect on biochemical, hematological and immunological parameters when compared with rosiglitazone. This may be attributed to the structural, genetic and pharmacokinetic alterations between pioglitazone and rosiglitazone.

CONCLUSIONS

To conclude, the present study has provided novel insights into the disease mechanisms of type 2 diabetes mellitus and possibly into new approaches for the prevention and treatment of type 2 diabetes mellitus and its complications.

Drug therapies, such as thiazolidinediones that address may of the comorbidities and metabolic dysfunctions associated with insulin resistance need
to be at the forefront of all healthcare professionals in treating type 2 diabetic mellitus patients.

Further line of work will be focused on the development of newer glitazone PPAR agonists that offer more advantage than the known thiazolidinediones as anti-diabetic agents.