INTRODUCTION

Diabetes is one of the most challenging health problems in the twenty first century (Rahman et al., 2009). Diabetes currently afflicts 171 million people worldwide (Boden and Taggart, 2009). According to the International Diabetes Federation (IDF), the number of people with diabetes in India is 40.9 million and is expected to rise to 69.9 million by 2025 (Ajay et al., 2008). Normal non-diabetic patients maintain plasma glucose <100 mg/dl in the fasting and <135 mg/dl in the post prandial period (Rossetti et al., 2008). Diabetes mellitus is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action or both (American Diabetes Association, 2009a).

Diabetes mellitus is classified as type 1, type 2, other specific types and gestational diabetes (American Diabetes Association, 2008). Type 1 diabetes is known as insulin dependent diabetes or Juvenile-onset diabetes and type 2 diabetes is known as non-insulin dependent or adult onset diabetes (American Diabetes Association, 2009b). A slowly progressive form of type 1 diabetes was acknowledged as latent autoimmune diabetes in adults (LADA) by the World Health Organization (WHO) and American Diabetes Association (ADA) (Van Deutekom et al., 2008).

Classification schemes define type 1 diabetes as a state of absolute insulin deficiency and type 2 as a state of insulin resistance combined with inadequate insulin secretion (Greenbaum et al., 2009). Type 1 diabetes is an autoimmune disease where auto reactive immune cells attack insulin producing β-cells, destroying insulin reserve leading to hyperglycemia (Eldor et al., 2009). The rate of loss of β-cell function is affected by factors like age at diagnosis, degree of metabolic control, immune status, genetics and marked inter-individual variation (Palmer, 2009). The symptoms of type 1 diabetes are significant weight loss and ketoacidosis (Ludvigsson et al., 2008).
Type 2 diabetes is a progressive disease characterized by declining β-cell function that in concert with insulin resistance, leads to loss of glycemic control and eventual diabetes complications (Nauck et al., 2009). The symptoms of type 2 diabetes are polyuria, polyphagia, blurred vision and general malaise (Goldfine, 2008).

Type 1.5 diabetes also known as latent autoimmune diabetes in adults (LADA) is an important form of diabetes although it is frequently under estimated (Mayer et al., 2007a). Type 1.5 diabetes is also known as slowly progressive type I diabetes, autoimmune diabetes in adults with slowly progressive β-cell failure, autoimmune diabetes not requiring insulin at diagnosis, autoimmune diabetes in adults and type 1.5 diabetes (Dunn et al., 2008). Type 1.5 diabetes has a later onset and slower progression towards an absolute insulin requirement (Cernea et al., 2009). Type 1.5 diabetes occurs in about 10% of patients classified as type 2 diabetes and not initially requiring insulin (Agardh et al., 2009). Diagnosis of type 1.5 diabetes is difficult due to lack of defining features (Jasem et al., 2010). The late age of presentation and absence of acute clinical symptoms like weight loss, ketosis and immediate insulin requirement of patients with type 1.5 diabetes often leads to their diagnosis as type 2 diabetes (Desai et al., 2007). The most common features of type 1.5 diabetes include age of patients < 35 years, non-obesity, insulin dependency, low C-peptide levels and positive glutamic acid decarboxylase antibodies (GADA) in a high percentage before and at onset of diabetes (Biesenbach et al., 2005). Screening for type 1.5 diabetes requires clinical suspicion which should be raised by a history of autoimmune disorders and lower body mass index (BMI), but it should not be excluded by elevated body mass index or family history of type 2 diabetes (Dunn et al., 2008). Antibodies to GAD65 (GADA) are considered highly predictive humoral markers of type 1.5 diabetes (Villalba et al., 2007). Determination of GADA represents the best
tool for a correct classification and a necessary prerequisite for a correct therapeutic appraisal (Genovese et al., 2006).

Auto immunity and insulin resistance co-exist in type 1.5 diabetes and the contribution of these factors seems to be reflected in GADA titres (Calsolari et al., 2008). The need for Insulin treatment is linked to the degree of autoimmunity and beta cell failure (Radtke et al., 2009). As complications and treatment regimens specific to type 1.5 diabetes are realized, improved means of identification of type 1.5 diabetes will become increasingly important (Chiu et al., 2007). GAD antibody is a marker of autoimmunity and C-peptide is a marker of β-cell dysfunction in type 1.5 diabetic patients (Genovese et al., 2006).

Long-term complications of diabetes mellitus are retinopathy, nephropathy, neuropathy and increased risk for cardiovascular disease (Horvath et al., 2007). Improved glycemic control reduces the risk of early microvascular complications such as retinopathy, nephropathy and neuropathy in patients with diabetes (Cefalu, 2005). Although the pathophysiological basis of these complications remains uncertain, hyperglycemia appears to play a central role (Diabetes Control and Complications Trial / Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group, 2005).

In India, limited studies have focused on diabetes care and provide an insight into the current profile of patients and their management (Venkataraman et al., 2009). Oral antidiabetic drugs (OAD) such as metformin is the first line of pharmatherapy for type 2 diabetes, which can elicit hypoglycemia. Other drugs are sulfonylureas and thiazolidiones (Nauck et al., 2007). The discovery of insulin more than 80 years ago is considered one of the greatest medical breakthroughs of the 20th century (Hirsch, 2005). The modern goals of insulin replacement in diabetes are HbA1c < 6.5% and prevention of hypoglycemia (Rossetti et al., 2008). Insulin analogs allow
patients greater flexibility in the timing of meals and exercise, thereby enhancing the quality of life (Shalitin and Phillip, 2007). Three slow acting insulin analogues like Aspart, Lispro and Glulisine are available (Siebenhofer-kroitzsch et al., 2009). Long acting insulin analogues like Glargine and Detemir have also been developed for the management of diabetes (Otto-Buczkowska et al., 2008). The Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have both proved the Exubera inhalation delivery system for the preprandial treatment of patients with diabetes (McMohan and Arky, 2007).

Type 1.5 diabetes is considered as the best prospect for assessment of tolerogenic immunotherapy (Groop et al., 2006). Treatment of type 1.5 diabetes should not only aim at obtaining good metabolic control, but also allow better preservation of the residual β-cell function. There are no current guidelines for treatment of type 1.5 diabetes, since this condition still has no clear definition (Cernea et al., 2009).

In autoimmune diabetes, there is destruction of insulin-producing pancreatic beta cells by a beta cell-specific autoimmune process (Yoon and Jun, 2005). The 90-kDa heat shock protein (Hsp90) plays an important role in conformational regulation of cellular proteins and thereby cellular signaling and function. As Hsp90 is considered a key component of immune function, its inhibition has become an important target for disease therapy (Bae et al., 2007).

Computer-based docking screens which are now widely used to discover new ligands for targets of known structure are common in molecular discovery (Kolb et al., 2009). In biomedical arena, computer-aided or in silico design which uses computational techniques in drug discovery and development process is being utilized to expedite and facilitate hit identification, hit-to-lead selection, optimize the absorption, distribution, metabolism, excretion and toxicity profile and avoid safety issues
Mangiferin, a major C-glucosylxanthone from *M. indica* stem bark, leaves, heartwood, roots and fruits occurs widely among different angiosperm families and ferns. Mangiferin was reported to show pharmacological activities namely antioxidant, immunomodulatory, anti-allergic, anti-inflammatory, antidiabetic and lipolytic properties, supporting the numerous traditional uses of the plant (Wauthoz et al., 2007).

An attempt was made in the present study for the differential diagnosis and treatment of the three types of diabetes- type 1, type 1.5 and type 2 with the following objectives:

1. Differential diagnosis of type 1.5 diabetes and type 2 diabetes
2. Comparative assessment of the complications of diabetes in type 1, type 1.5 and type 2 diabetes
3. Identification of suitable treatment strategies in different types of diabetes
4. Prognostic assessment of the control of the complications of different types of diabetes
5. *In silico* drug designing for type 1.5 diabetes.