



Navigating Diabetes Mellitus: Advancing Forward

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Diabetes Mellitus (DM) is a group of metabolic diseases characterized by an elevated blood glucose level – resulting from defects in insulin secretion, in insulin action or both. Diabetes Mellitus is not a pathogenic entity but a group of etiologically different metabolic defects that share the phenotype of hyperglycemia. Several distinct types of DM exist and are caused by complex interaction of genetic factors and life style choices. The metabolic dysregulation associated with DM causes secondary pathophysiologic changes in multiple organ systems that impose a tremendous burden on the individual with diabetes and on the health care system. Intensive diabetes management has set the goal of improvement of glycemic control, which reduces complications associated with the diseases. A strict control of blood glucose levels (Ideally HbA1c < 7% mean plasma glucose level, < 150 mg/dl) delays the onset and progression of diabetic neuropathy, nephropathy, retinopathy, and reduction in cardiovascular risk. Sulfonylureas (Glibenclamide, Gliclazide, Glemiperide, and tolbutamide), Biguanides (Metformin, Phenformin) are effectively used in controlling elevated blood glucose levels in oral antidiabetic therapy. . Sitagliptin is a once-daily, orally active, potent and highly selective dipeptidyl peptidase-4 (DPP-4) inhibitor approved in many countries for the treatment of patients with type- 2 diabetes. Sitagliptin was the first DPP-4 inhibitor that was approved for the management of type 2 diabetes in 2007. Sitagliptin is being used as monotherapy (100 or 200 mg OD) or as an add-on to ongoing oral antidiabetic agents (OAD) in patients with type 2 diabetes with significant reduction in glycaemic levels within a few weeks. In this review, we will briefly study the different therapeutic options available for the management of Diabetes Mellitus.

Keywords: Diabetes mellitus, Insulin, Sulfonylureas, Biguanides, Sitagliptin.

Introduction

Diabetes Mellitus (DM) comprises a cluster of metabolic disorders characterized by elevated blood glucose levels, stemming from deficiencies in insulin secretion, insulin action, or a combination of both [1-5]. Rather than constituting a singular pathogenic entity, DM encompasses various etiological metabolic defects that share the common feature of hyperglycemia. Different types of DM arise from complex interactions involving genetic factors and lifestyle choices, contributing to hyperglycemia through reduced insulin secretion, decreased glucose utilization, and increased glucose production [5-10]. The metabolic dysregulation associated with DM leads to secondary pathophysiological changes across multiple organ systems, placing a significant burden on individuals with diabetes and on healthcare systems. In the United States, DM stands as the primary cause of end-stage renal disease, non-traumatic lower extremity amputations, and adult blindness. With a rising global incidence, DM is projected to remain a leading cause of morbidity and mortality in the foreseeable future [10-15]. Approximately 20% of the current global diabetic population resides in the South-East Asian region, and it is anticipated that the number of individuals with diabetes in this region will triple by 2025, escalating from an estimated 30 million

to 80 million. Consequently, South-East Asian countries are expected to face substantial challenges and bear the maximum global burden of the disease in the initial decades of the 21st century [15-20]. An examination of age-specific prevalence rates consistently reveals an increase in diabetes prevalence with advancing age. In the South-East Asian region, the proportion of individuals aged 30 years and above rose from 37.2% in 1995 to 41.9% in 2005, corresponding to an increase in the proportion of diabetics in older age groups. Unfavorable modifications in lifestyle and dietary habits associated with urbanization are considered pivotal factors in diabetes development. Diabetes prevalence is approximately twice as high in urban areas compared to rural populations. The percentage of diabetic cases residing in urban areas is projected to increase from 5.4% in 1995 to 7.3% by 2025. Recent population-based surveys in Bangladesh, India, and Indonesia indicate a considerable rise in the prevalence of the disease in both urban and rural populations compared to earlier results [20-25].

Classification of Diabetes Mellitus:

Diabetes Mellitus is categorized based on the underlying pathogenic processes that result in hyperglycemia, with the two primary classifications being Type 1 and Type 2 DM [25].

Type 1 diabetes: Predominantly occurring in childhood, Type 1 diabetes constitutes approximately 10 to 20% of diagnosed diabetes cases. This form of diabetes is characterized by a near-total deficiency of insulin due to the destruction of pancreatic beta cells. The causes of beta cell destruction may involve autoimmunity, viral infections, or drug-related factors [26-29].

Type 2 diabetes: Representing a heterogeneous group of disorders, Type 2 diabetes involves varying degrees of insulin resistance, impaired insulin secretion, and heightened glucose production. Common phenotypic hyperglycemia in Type 2 DM arises from distinct genetic and metabolic defects affecting insulin action and/or secretion. The onset of Type 2 DM is often preceded by a phase of abnormal glucose homeostasis categorized as impaired fasting glucose (IFG) or impaired glucose tolerance (IGT) [30-35].

Other types of diabetes mellitus:

1. **Gestational Diabetes Mellitus:** This form manifests as glucose intolerance during pregnancy. Insulin resistance linked to the metabolic changes in late pregnancy increases insulin requirements and may result in impaired glucose tolerance.
2. **Maturity Onset Diabetes of the Young (MODY):** MODY is a subtype of DM characterized by autosomal dominant inheritance, an early onset of hyperglycemia, and impairment in insulin secretion [36-40].

Patient Complaints of Symptoms Suggesting DM.

Test Urine for Glucose and Ketones.

Measure Random or Fasting Blood Glucose. Diagnosis Confirmed by:

- Fasting Plasma Glucose > 7.0 mmol/l
- Random Plasma Glucose >11.1 mmol/l

Indication for Oral Glucose Tolerance Test.

- Fasting Plasma Glucose 6.1-6.9 mmol/l
- Random Plasma

Figure 1. Diagnosis of DM [40-45]

Diabetes	Plasma Glucose	Whole Blood
	Venous (Capillary) (mmol/l)	Glucose Venous (Capillary) (mmol/l)
Fasting	>7.0	>6.1
2 Hours after Glucose Load.	>11.1 (>12.2)	>10.0 (>11.1)
Impaired Glucose Tolerance		
Fasting	<7.0	<6.1
2 Hours after Glucose Load.	7.8-11.0 (8.9-12.1)	6.7-9.9 (7.8-11.0)

Table 1. Oral Glucose Tolerance Test: WHO Diagnostic Criteria [46-49]

Management of Diabetes Mellitus

Once diabetes mellitus (DM) is diagnosed, the treatment objective is to regulate blood glucose levels and prevent complications. Depending on the type of DM, this can involve regular physical exercise, a carefully controlled diet, and medication. Individuals with Type 1 DM typically require insulin injections, often administered two to four times daily, as their bodies do not produce insulin [49-55]. The required insulin amount varies among individuals and can be influenced by factors such as physical activity levels, diet, and the presence of other health conditions. People with Type 1 DM must monitor their glucose levels multiple times a day to maintain control. For those with Type 2 DM, treatment initially involves diet control, exercise, and weight reduction, although over time, these measures may become insufficient. Individuals with Type 2 DM often collaborate with nutritionists to develop a diet plan regulating blood sugar levels, particularly after meals [55-60].

A recommended meal typically contains low fat (30% or less of total calories), moderate protein (10 to 20% of total calories), and a variety of carbohydrates from sources like beans, vegetables, and grains. Regular exercise, even in short durations, aids in glucose absorption by body cells. Diet control and exercise may also contribute to weight reduction, partially mitigating the body's insulin utilization challenges [60-65]. Intensive diabetes management aims to enhance glycemic control, reducing complications associated with the disease. Strict control of blood glucose levels (preferably HbA1c < 7%, mean plasma glucose < 150 mg/dl) delays the onset and progression of diabetic complications like neuropathy, nephropathy, retinopathy, and lowers cardiovascular risk [12]. Various medications, including sulfonylureas (such as Glibenclamide, Gliclazide, Glemiperide, and tolbutamide) and biguanides (like Metformin and Phenformin), effectively control elevated blood glucose levels in oral antidiabetic therapy.

Sulfonylureas stimulate pancreatic beta-cells to produce insulin, enhance cellular glucose uptake, and reduce liver glucose production. They bind to the sulfonylurea receptor on pancreatic B-cells, blocking ATP-sensitive potassium channels, leading to decreased potassium efflux and β cell depolarization. The subsequent opening of voltage-dependent calcium channels causes calmodulin activation, resulting in insulin exocytosis from granules [65-70]. However, sulfonylureas can lead to weight gain and hypoglycemia [76].

Metformin and phenformin, both biguanides, are utilized in oral diabetic therapy. Metformin significantly improves glycemic control and lipid profiles, primarily by inhibiting gluconeogenesis [77-81]. Acarbose effectively controls postprandial blood glucose levels [82-83]. The global burden of diabetes is increasing due to rising incidence and prevalence, particularly of type-2 diabetes, driven by factors like aging populations, obesity, physical inactivity, and increased longevity of patients with diabetes. Type 2 DM management is complex, involving various pharmacological agents. It is a significant risk factor for microvascular and macrovascular complications,

emphasizing the need for glycemic control. Available antidiabetic agents target different mechanisms to improve blood glucose levels, but each has its tolerability and safety concerns. Monotherapy may be insufficient for long-term glycemic control, necessitating combination therapies. Sitagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor, is used for type 2 diabetes management, enhancing incretin hormones' gluco-regulatory effects [90-105].

Conclusion

Despite the array of available options, modern medicine has encountered limited success in combating Diabetes Mellitus. While the condition cannot be completely cured, effective management is achievable through the judicious use of available therapeutic interventions. Despite lifelong efforts by investigators and scientists, a definitive cure or eradication medicine remains elusive. The current drugs and medications are capable of controlling the disease, yet a comprehensive cure remains absent. The understanding of the "GENOME" offers a glimmer of hope for prevention, but extensive work remains, especially given its significant hereditary component. Consequently, Diabetes Mellitus stands as a condition that necessitates enduring management. Ongoing advancements in genetic studies, particularly in genome coding, may emerge as potential solutions in the future. Otherwise, the upcoming generation may continue to grapple with the persistence of the disease in the community.

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