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MANAGING DIABETES MELLITUS: A WAY FORWARD

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Abstract:

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 (Glebenclemide, Gliclazide, Glemiperide, and tolbutamide), Biguandies (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.

Key words: *Diabetes mellitus, Insulin, Sulfonylureas, Biguanides, Sitagliptin.*

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INTRODUCTION:

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. Depending on the etiology of DM, factors contributing to hyperglycemia may include reduced insulin secretion, decreased glucose utilization and increased glucose production [1,2]. 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. In the United States, DM is the leading cause of end stage renal disease, non-traumatic lower extremity amputations and adult blindness, with an increasing incidence worldwide, DM will be a leading cause of morbidity and mortality for the foreseeable future [3]. It is estimated that 20 per cent of the current global diabetic population resides in the South-East Asian region. The number of diabetic persons in the countries of the region is likely to triple by the year 2025, increasing from the present estimates of about 30 million to 80 million. With these projected increase in the diabetic population in future, South East Asian countries will become the most challenged region in the world and the region will bear the maximum global burden of the disease in the initial decades of the 21st century [4]. An analysis of age-specific prevalence rates of diabetes mellitus consistently showed an increase in prevalence with increasing age. In the South East Asian region, the proportion of people in the age group 30 years and above is increased from 37.2 percent in 1995 to 41.9 percent in 2005 and there is a corresponding increase in the proportion of diabetics in older age groups. Unfavorable modification of lifestyle and dietary habits that are associated with urbanization are believed to be the most important factors for the development of diabetes. The prevalence of diabetes is approximately twice in urban areas than in rural population. The percentage of diabetic cases residing in urban areas is projected to increase from 5.4 percent in 1995 to 7.3 percent by the year 2025. Population-based surveys completed recently in Bangladesh, India and Indonesia have shown considerable increase in the prevalence rate of the disease in both urban and rural dwellers when compared to results obtained earlier [5].

CLASSIFICATION OF DIABETES MELLITUS [5]:

Diabetes Mellitus is classified on the basis of the pathogenic process that leads to hyperglycemia. The two broad categories of DM are designated as Type 1 and Type 2 DM [5].

Type 1 diabetes: Type 1 diabetes mainly occurs in childhood and accounts for about 10 to 20 % of known diabetics. The disease is characterized by almost total deficiency of insulin due to destruction of beta cells of the pancreas. The beta cell destruction may be caused by autoimmunity, viruses or drugs.

Type 2 diabetes: Type 2 diabetes is a heterogeneous group of disorders characterized by variable degrees of insulin resistance, impaired insulin secretion and increased glucose production. Distinct genetic and metabolic defects in insulin action and/or secretion give rise to common phenotypic hyperglycemia in type 2 DM. Type 2 DM is preceded by a period of abnormal glucose homeostasis classified as impaired fasting glucose (IFG) or impaired glucose tolerance (IGT) [5].

Other types of diabetes mellitus:

Gestational Diabetes Mellitus – Glucose intolerance may develop during pregnancy. Insulin resistance related to the metabolic changes of late pregnancy increases insulin requirements and may lead to IGT.

Maturity Onset Diabetes of the Young (MODY) - is a subtype of DM characterized by autosomal dominant inheritance, early onset of hyperglycemia and impairment in insulin secretion [5].

Table 1: Diagnosis of DM [6-9].

Patient Complains 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/1

* Random Plasma Glucose >11.1 mmol/1 Indication for Oral Glucose Tolerance Test.

* Fasting Plasma Glucose 6.1-6.9 mmol/1

* Random Plasma

Table 2: Oral Glucose Tolerance Test: WHO Diagnostic Criteria [6-9].

	Plasma Glucose Venous (Capillary) (mmol/1)	Whole Blood Glucose Venous (Capillary) (mmol/1)
Diabetes		
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)

MANAGEMENT OF DIABETES MELLITUS:

Once DM is diagnosed, treatment consists of controlling the amount of glucose in the blood and preventing complications. Depending on the type of DM, this can be accomplished through regular physical exercise, a carefully controlled diet, and medication. Individuals with Type 1 DM require insulin injections, often two to four times a day, to provide the body with the insulin as it is not produced. The amount of insulin needed varies from person to person and may be influenced by factors such as a person's level of physical activity, diet, and the presence of other health disorders. In order to control insulin levels, people with Type 1 DM must monitor their glucose levels several times a day. For persons with Type 2 DM, treatment begins with diet control, exercise and weight reduction, although over time this treatment may not be adequate. People with Type 2 DM typically work with nutritionists to formulate a diet plan that regulates blood sugar levels so that they do not rise too swiftly after a meal. A recommended meal is usually low in fat (30 %or less of total calories), provides moderate protein (10 to 20 % of total calories), and contains a variety of carbohydrates, such as beans, vegetables, and grains. Regular exercise helps body cells to absorb glucose - even ten minutes of exercise a day can be effective. Diet control and exercise may also play a role in weight reduction, which appears to partially reverse the body's inability to use insulin [10-11].

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 [12]. Sulfonylureas (Glebenclemide, Gliclazide, Glemiperide, and tolbutamide), Biguandies (Metformin, Phenformin) are effectively used in controlling elevated blood glucose levels in oral antidiabetic therapy. Sulfonylureas stimulate pancreatic beta-cells for the production of insulin as well as they increase cellular uptake and utilization of glucose, and decrease glucose production in the liver.They effectively bound with sulfonyl urea receptor on the surface of pancreatic B-cells [13-16] .This binding subsequently blocks the ATP sensitive potassium channels results in decreased potassium efflux and depolarization of β cells. The opening of voltage-dependent calcium channels in the β cell cause calmodulin activation, which in turn leads to exocytosis of insulin from the granules [17].

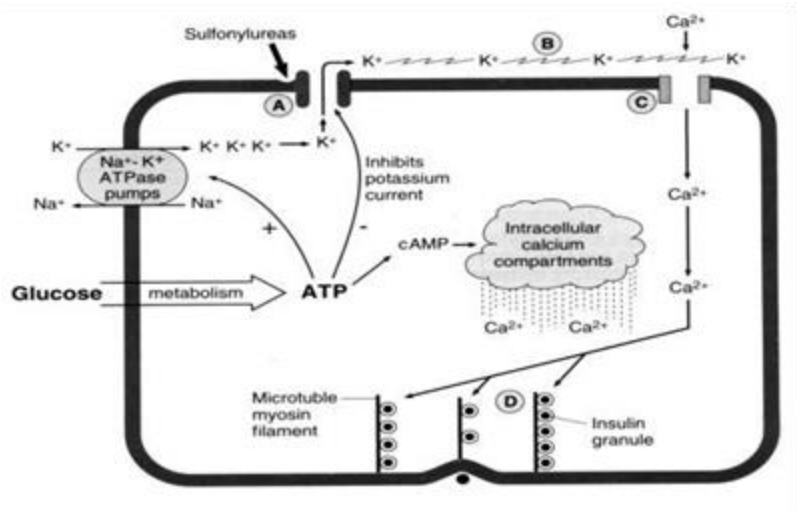

Figure 1: Insulin secretagogues action of Sulfonylureas [12-17]

Weight gain and hypoglycemia are the adverse effects associated with sulfonylureas [18]. The insulin secretagogues action of sulfonylureas does not depend on plasma glucose levels. The sulfonylurea monotheraphy produces an average reduction in hemoglobin A1c concentrations of about 1.0%-1.5%. metformin, and phenformin have been employed for oral diabetic therapy. Metformin significantly improves glycemic control, lipid profile [19-21]. It majorly inhibits gluconeogenesis [(34)] .Acarbose effectively control the postprandrial blood glucose levels [22-23].

This high global burden is continuously on the rise with increasing incidence and prevalence of type -2 Diabetes mellitus due to increasing population age, obesity, and physical inactivity as well as by the increasing longevity of patients with DM and accounts for almost 90% of patients with the disease both in developing and developed countries [24]. In type 2 DM glycemic management has become increasingly complex and, to some extent, controversial, with a wide array of pharmacological agents now available [25-29]. Type 2 DM is a major risk factor for developing both microvascular (retinopathy, nephropathy and neuropathy) and macrovascular complications (coronary heart disease, cerebrovascular disease and peripheral vascular disease) [30]. Variable treatments focus on reducing hyperglycemia and improving insulin sensitivity. These modalities are attractive in theory, as they appear to target the primary defects associated with type 2 DM. However, despite the wide array of treatment options available, glycemic control declines over time [31]. Unattainable glycemic control is often a result of ongoing deterioration of beta-cell function. The primary goal of treatment is to target glycemic control by maintaining the HbA1c level at 6-7% to decrease the incidence of microvascular and macrovascular complications without predisposing patients to hypoglycemia. Currently available antidiabetic agents work by different mechanisms to improve blood glucose levels. Unfortunately, each of them has its tolerability and safety concerns that limit its use and dose titration [32-34].

Monotherapy treatment with a single antihyperglycaemic agent is often unsuccessful at achieving and/or maintaining long-term glycaemic control in patients with type -2 diabetes, so many patients require combination therapies [35]. Monotherapy with metformin or a sulphonylurea is the most commonly used as ainitial oral hypoglycaemic agent (OHA) regimen to treat patients with type 2 diabetes. Sulphonylureas improve blood glucose level by stimulating insulin secretion from pancreatic b-cells in a non-glucose–dependent manner [36]. Metformin, a biguanide, acts primarily by lowering hepatic glucose production and may also improve insulin resistance [37-38]. As with all OHAs, monotherapy with a sulphonylurea may not achieve or maintain glycaemic control; therefore novel, efficacious and well-tolerated therapies that can be added to a sulphonylurea agent are needed. Similarly, dual combination therapy with a sulphonylurea agent and metformin also may not achieve or maintain glycaemic control [35, 39]. In this setting, use of insulin is often the next therapeutic step, although triple OHA therapy [e.g.adding a thiazolidinedione, a peroxisome proliferator–activated receptor g (PPARg) agent, to ongoing dual therapy with metformin and a sulphonylurea] is increasingly being used in clinical practice. Insulin requires parenteral administration, which many patients find undesirable and the

addition of a thiazolidinedione can lead to oedema and an increase in body weight. Hence, there is a need for additional OHA options that can be added to the dual combination of sulphonylurea and metformin to avoid the need to switch to insulin. 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 [40]. 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 [41].

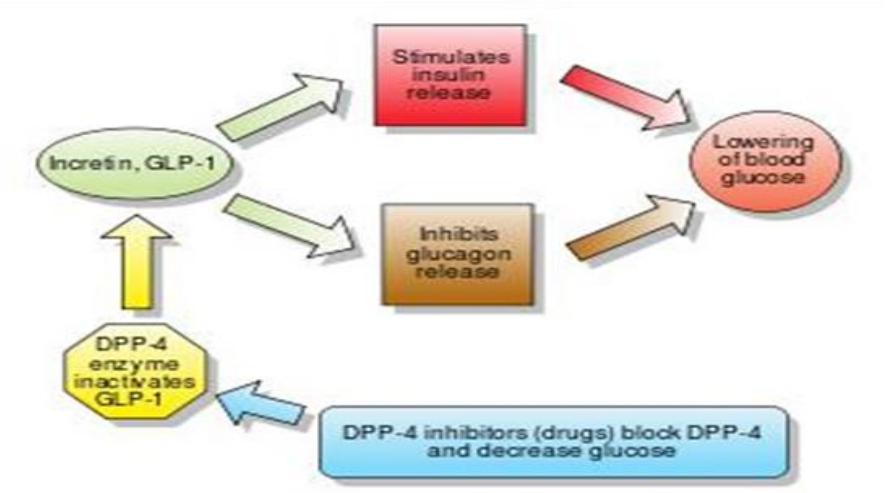

Fig 2: Mechanism of action of DPP-IV inhibitors [42-46]

DPP-4 is an enzyme cause degradation of the intact (active) incretin hormones, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP) to inactive metabolites.GLP-1 and GIP are released by the intestine into the circulation in response to a meal, and both hormones increase glucose-dependent insulin secretion; in addition,GLP-1 suppresses glucagon release. By inhibiting the degradation of active incretins, sitagliptin increases active incretin concentrations, thereby enhancing their gluco regulatory effects [42-46]. Sitagliptin, administered as monotherapy or as add-on therapy to metformin or to a PPARg agent, has been shown to improve glycaemic control and is well tolerated in patients with type 2 diabetes [12, 47-50].

CONCLUSION:

In spite of all these options available, the modern medicine has achieved very limited success against it. Diabetes Mellitus cannot be cured fully but can be managed with the appropriate use of therapeutic options available. Whereas many investigators and scientists have been working lifelong but could not evolve a cure or medicine for its eradication. The best available drugs and medicines can only control the disease but yet no cure is available. At present knowledge of "GENOME" does impart a ray of hope for its prevention but yet lot is to be done as it is one of the major hereditary diseases. Thus it happens to be a disease which is to be endured with its control. Recent advances in genetic studies with genome coding may prove to be one of the answers in the times to come, otherwise, the on-coming generation will continue to maintain the disease in the community.

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