

DIABETES MELLITUS: A REVIEW WITH EDGE OF SGLT2 INHIBITORS

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ABSTRACT

The relative (Type 2 DM) or absolute (Type 1 DM) deficiency of insulin hormone could result into hyperglycemia, which is a characteristic feature of diabetes mellitus. Diabetes mellitus is a leading cause of morbidity and mortality because of its associated complications viz. Neuropathy, Nephropathy, Retinopathy, Cardiovascular disorders.

The feature which has to be noted down is the death of individuals before the age of 70 y, which is attributable to high blood glucose levels. According to WHO diabetes mellitus will be the seventh leading cause of deaths till 2030.

The induction of glycosuria as meant for glycaemic control in patients with DM is an extension of the physiological role of renal TmG to curb the menace of hyperglycemia. The first biologically derived SGLT2 inhibitor phlorizin, isolated in 1835 from the root bark of apple tree, was not developed as an antihyperglycaemic drug because of rapid degradation by lactase-phlorizin hydrolase and poor absorption from the gastrointestinal tract. Other glycoside moieties derived from phlorizin structure have subsequently been developed recently.

Keywords: Diabetes mellitus, EDGE of SGLT2 inhibitors

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INTRODUCTION

The relative (Type 2 DM) or absolute (Type 1 DM) deficiency of insulin hormone could result into hyperglycemia, which is a characteristic feature of diabetes mellitus [1]. Diabetes mellitus is a leading cause of morbidity and mortality because of its associated complications viz. Neuropathy, Nephropathy, Retinopathy, Cardiovascular disorders [2, 3]. The glycemic control if not well managed, which is mainly due to hyperglycemia, can affect every system of the body [1]. Especially in developing countries, 80% of diabetes are contributing to deaths. According to WHO, 316 million people has been suffering from dm worldwide. A look at WHO report, suggests that India is leading the world with over 32 million patients and likely this number will be projected increase to 79.4 million by the year 2030 [4]. The SGLT2 inhibitors class includes sergliflozin, remogliflozin, ipragliflozin, and empagliflozin.

Epidemiology

The alarming rise has reached up to 422 million in 2014 from 108 million in 1980 [5]. The gross prevalence of diabetes has risen up to 8.5% in 2014 from 4.7% in 1980 [5]. An estimated 1.6 million deaths were caused by diabetes mellitus in 2015. The feature which has to be noted down is the death of individuals before the age of 70 y, which is attributable to high blood glucose levels. According to WHO diabetes mellitus will be the seventh leading cause of deaths till 2030 [5].

Etiological classification of diabetes mellitus

Type 1 DM (β cell destruction leading to deficiency of insulin), can be classified into Idiopathic DM and Immune-mediated DM [6]. The Type 2 DM (predominantly secretory defect with insulin resistance to a relative insulin deficiency with insulin resistance). Other specific types of DM: Genetic abnormalities of β -cells functions: attributed in Mitochondrial DNA, Chromosome 17, HNF-1 β (MODY5), Chromosome 13, Insulin promoter factor-1 (IPF-1; MODY4), Chromosome 20 HNF-4 α (MODY3), Chromosome 7, Glucokinase (MODY2). The genetic abnormalities in actions of insulin can lead to Lipoatrophic diabetes, Rabson-mendenhall syndrome. Leprechaunism, Type An insulin resistance. The exocrine pancreatic disorders could result in Fibrocalculus pancreatopathy, Cystic fibrosis, Neoplasia, Pancreatitis,

Trauma/pancreatectomy, Haemochromatosis. Further other endocrinological disorders which include Acromegaly, Cushing's syndrome, Aldosteronoma, Somatostatinoma, Hyperthyroidism, Glucagonoma, Pheochromocytoma are attributable causes for DM. The Chemical or drug-induced DM can be due to Dilantin, Thiazides, B-adrenergic agonists, Diazoxide, Thyroid hormone, Nicotinic acid, Vacor, Pentamidine, V-interfeon, Glucocorticoids. Although DM can be gestational origin also.

Pathophysiology of DM

The direct co-relationship between behavioral and physiological responses and hyperglycemia is relatively direct. Whenever hyperglycemia is there, the brain ensues immediately, and an message is sent through nerve impulses to organs and pancreas to reduce its effects. Type 1DM: In type 1 DM, there is an autoimmune destruction of insulin-producing cells in the pancreas by CD4+and CD8+T cells and macrophages infiltrating islets of Langerhans. This eventually leads to a reduction in the secretion of insulin. Additionally, pancreatic α cells work functions become abnormal and excess release of glucagon in T1DM. Otherwise reduced secretion of glucagon is there in hyperglycemia, but in type 1dm this does not happens. In Type 2 DM: The impairment of insulin secretion by default of dysfunction of pancreatic β cell and insulin resistance resulting in impaired insulin action. Although the insulin resistance may be overpowered by mass of β cells, which are enough capable of more amounts of insulin, but the overpowered by mass of β cells, which are enough capable of more amounts of insulin, but the plasma insulin concentration is insufficient to maintain normal blood glucose homeostasis²⁰. The hyperinsulinemia and insulin resistance eventually leads to impaired glucose tolerance.

Management

The weight loss, exercise, and off course diet are the most important aspects while management of patients of DM. The pharmacotherapy may include the prescription regime consisting of either alone as a single drug or multidrug combinations viz. Sulphonylureas, Meglitinide analogues, Biguanides, Thiazolidinedione's, α -Glucosidase inhibitors, Glucagon-like peptide-1 (GLP-1) receptor

agonists and Dipeptidyl-peptidase-4 (DPP-4) inhibitors. As well as insulin therapy used for primary or secondary failure of oral agents.

The co-morbid disorders viz cardiovascular diseases (HTN, CAD, and Hyperlipidemia) and other complications like Diabetic Neuropathy; Diabetic Nephropathy, etc must be treated simultaneously to improve outcomes and prognosis of management of DM.

a) Insulin therapy: to lower blood glucose levels, injectable insulin acts similarly as endogenous insulin.

The three type of insulin preparations available are: Rapid-acting: which includes Insulin glulisine, Insulin lispro, Insulin aspart all are having the onset of 5-15 min with reaching peak concentrations within 45-75 min and duration of action is between 2-4 h. The Short-acting includes insulin regular having onset of ~30 min with reaching peak concentrations within 2-4 h and duration of action is between 5-8 h. further Intermediate-acting consists of Insulin isophane having the onset of 1.5-2 h with reaching peak concentrations within 4-12 h and duration of action is between 18-28 h. The last category includes long-acting insulins comprising of insulin glargine having onset of 1-3 h and duration of action is between 20-24+h, insulin lispro having onset of 5-15 min with reaching peak concentrations within 45-75 min and duration of action is between 6-24+h, insulin aspart having onset of 5-15 min with reaching peak concentrations within 45-75 min and duration of action is up to 36 h, insulin degludec having onset of 1-3 h and duration of action is between 40+h.

b) Oral drugs for type 2 DM: Sulfonylureas: act by stimulating the pancreas to release more insulin and only effective when pancreatic beta-cell activity is still present. 1st generation includes Chlorpropamide, Tolazamide, Tolbutamide. The second generation comprised of Gliclazide, Glimperide, Glyburide, Gliclazide. Further oral pharmacotherapy may include Biguanides: Metformin which acts by: inhibiting amount of glucose produced by the liver, increasing insulin-receptor binding, Stimulating tissue uptake of glucose. The Alpha-Glucosidase Inhibitors: miglitol and acarbose, Alpha-Glucosidase inhibitors slows the digestion of carbohydrates and thus, delay absorption of glucose. They acts by inhibiting the intestinal enzymes that digest carbohydrates, thereby reducing the carbohydrate digestion after a meal, which lowers postprandial (after a meal) blood sugar elevation in diabetics. The very much commonly used Thiazolidinedione's: Pioglitazone and Rosiglitazone, Thiazolidinedione's (also called Glitazones) work by making body's cells more sensitive to insulin. Thus less insulin is needed to move glucose from the blood into cells. This leads to a reduction of blood glucose levels [7].

C) SGLT2 inhibitors

The induction of glycosuria as meant for glycaemic control in patients with DM is an extension of the physiological role of renal TmG to curb the menace of hyperglycemia. The first biologically derived SGLT2 inhibitor phlorizin, isolated in 1835 from the root bark of apple tree, was not developed as an antihyperglycaemic drug because of rapid degradation by lactase-phlorizin hydrolase and poor absorption from gastrointestinal tract [8]. Other glycoside moieties derived from phlorizin structure have subsequently been developed recently. The another group of C-aryl glycosides, discovered by Ellsworth *et al.* includes dapagliflozin and canagliflozin characterized by the resistance to degradation by β -glucosidase enzymes in the gastrointestinal tract [9-11]. Dapagliflozin is ~1,200-times more selective for SGLT2 than for SGLT1. It inhibits the renal glucose reabsorption by estimated 40-50%, with the maximum amount of excreted glucose of 80-85 g/day [10, 12]. The Clinical studies of dapagliflozin as monotherapy or combination therapy with metformin or insulin in patients of T2DM have confirmed its efficacy in reducing fasting as well as postprandial glucose and HbA1c parameters [13-15]. The pharmacokinetics and the bioavailability of Dapagliflozin are not altered by high-fat meal; Also, no interactions with other class of drugs commonly used in pharmacotherapy of T2DM have been reported [16, 17].

Future perspectives

The absolute lifestyle modifications, the effective pharmacotherapy with rational drug use must be implemented. The permanent leftover of smoking, alcohol, tobacco and narcotic products must be given up completely to improve patient's perspectives of DM. The Acute administration of SGLT2 inhibitors reduces both preprandial and postprandial blood glucose levels, and chronic administration may lead to a decrease of glucotoxicity.

AUTHORS CONTRIBUTIONS

All the author have contributed equally

CONFLICT OF INTERESTS

Declared none

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