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SGLT-2 Inhibitors and GLP-1 Receptor agonist on Cardiovascular mortality reduction

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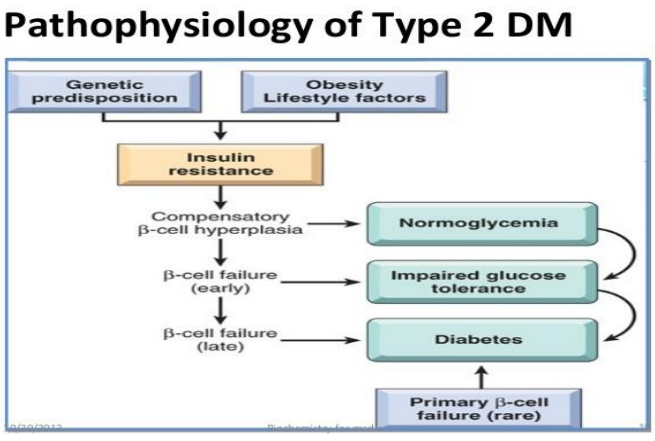
Abstract: **Type 2 DM is a prevailing chronic disease worldwide. It is associated with a number of complications and has very significant mortality and morbidity as well. The main pathophysiology of diabetes is the understanding of carbohydrate metabolism. Insulin resistance, mainly caused by obesity and physical inactivity, both precedes and predicts type 2 diabetes. This insulin resistance is commonly due to metabolic factors other than Weight, Fat distribution, Race, Inactivity, Family history, Age, Prediabetics, Areas of darkened skin, usually in the armpits and neck and Gestational diabetes. DM-2 is also associated with a number of complications like Heart and blood vessel disease, Nerve damage (neuropathy) and kidney damage. Metformin remains the first line and most effective medication, yet it is not the best use as a single drug regime in most of the patients. Nowadays the most effective treatment in Type 2DM is a combination of multiple oral hypoglycemic drugs. SGLT-2 Inhibitors and GLP-1 Agonist are some of the efficacious 2nd line treatments for Type 2 DM. One of the most important questions is what are the factors that should be taken into account to guide the choice between SGLT-2 inhibitors and GLP-1 Agonists. It is estimated that Both GLP-1 Agonist and SGLT-2 Antagonist are beneficial in reducing the number of complications especially associated with cardiovascular outcomes. SGLT-2 Inhibitors are particularly more efficacious in preventing cardiovascular risks.**

Keywords: **SGLT-2 Inhibitors, GLP-1, pathophysiology, cardiovascular risks.**

1. INTRODUCTION

Diabetes Mellitus

- Main element in the pathophysiology of diabetes is the understanding of carbohydrate metabolism. Normally after food consumption, the carbohydrates are broken down into tiny small tiny glucose molecules and this glucose after getting reabsorbed into the blood raises the blood glucose levels. In response to these raised blood glucose levels more and more insulin gets secreted from the pancreatic B cells and that helps in the transport of glucose into most of the cells through the insulin mediated transporters. Subsequent use of glucose by the cells under the effect of insulin results in lower blood glucose levels, this will further lead to decreased insulin level (3).



Insulin resistance, mainly caused by obesity and physical inactivity, both precedes and predicts type 2 diabetes. This insulin resistance is commonly due to metabolic factors.

In type 2 diabetes mellitus, metabolic syndrome is associated with an increased risk of cardiovascular disease and mortality, the main complication of type 2 diabetes. The development of type 2 diabetes, overt hyperglycemia, also requires the presence of a relative deficiency in insulin secretion from the pancreas. Genetic risk factors play a major role in the development of this insulin resistance (2).

Risk factors for Type 2 DM

Factors that may increase your risk of type 2 diabetes include:

- Weight
- Fat distribution
- Race
- Inactivity
- Family history
- Age
- Prediabetics
- Areas of darkened skin, usually in the armpits and neck
- Gestational diabetes
- Polycystic ovarian syndrome (2).

Complications

Some of the potential complications of Type 2 Diabetes Mellitus include:

- Heart and blood vessel disease
- Nerve damage (neuropathy)
- Kidney damage
- Eye damage
- Hearing impairment
- Skin conditions
- Slow healing
- Sleep apnea
- Alzheimer's disease

Prevention

A healthy lifestyle can help prevent type 2 diabetes. In Prediabetics, lifestyle changes can decrease the progression of diabetes. A healthy lifestyle includes:

- Eating healthy foods
- Getting active
- Losing weight.
- Avoiding a sedentary lifestyle.

Treatment options

When diet and exercise alone aren't enough to keep their blood sugar in a healthy range, people very often try oral hypoglycemic agents. A table of most commonly agents used are depicted below (4).

Table 1 – Non-insulin agents available for treatment of diabetes in the United States

Drug class	Route of administration	Advantages	Disadvantages	Comments	Reduction in HbA_{1c} achieved as monotherapy (percentage points)
Biguanides	Oral	Effectively lowers HbA_{1c}, low cost, does not cause weight gain	GI complaints, minimal risk of lactic acidosis (contraindicated in patients older than 80 y and in those with elevated creatinine levels)	Metformin is the best initial drug for treatment of type 2 diabetes	1 - 1.5
Sulfonylureas	Oral	Available as generics (low cost)	Can cause weight gain	Appropriate add-on therapy when metformin alone (at maximum dosage) is insufficient; glimepiride has a better safety profile in patients with renal disease	1 - 1.5
Disaccharidase inhibitors	Oral	Do not promote weight gain; safe in patients with renal failure; reinforce carbohydrate restriction through averse response	Flatulence, abdominal discomfort, diarrhea; relatively high cost	Good monotherapy agent in elderly patients with constipation, obese patients	0.6 - 1
Thiazolidinediones	Oral	May preserve beta cells from ongoing destruction	Cause fluid retention (sometimes leading to heart failure); stimulate accumulation of adipose tissue	Best used in patients who can maintain strict dietary control	1 - 1.5
Meglitinides	Oral	Rapid disappearance time results in lower risk of hypoglycemia than with sulfonylureas	Much shorter duration of action than sulfonylureas; thus, these agents must be taken before meals; moderately high cost	Useful in elderly patients, cardiac patients, and others in whom hypoglycemia is a significant risk	1 - 1.5
GLP analogs	Parenteral	May result in progressive weight loss in some patients	Nausea (often severe); must be injected twice daily; high cost	Typically used with hope of weight loss in very obese patients	0.8 - 1
Amylin analogs	Parenteral	Weight loss can occur	Nausea; unpredictable hypoglycemia; high cost	May be useful for inducing satiety at big meals	0.6 - 0.8
DPP-IV inhibitors	Oral	No prominent side effects, low risk of hypoglycemia	Does not lead to weight loss; high cost	Can be useful when added to metformin	0.6 - 1.2

HbA_{1c}, glycosylated hemoglobin; GLP, glucagonlike peptide; DPP-IV, dipeptidyl peptidase IV.

Comparison of SGLT-2 and GLP-1

Outcome	GLP-1 receptor antagonists	SGLT2 inhibitors
A1c reduction (%)	0.7–1.7	0.32–1.17
Target of BG lowering	Shorter acting, mostly postprandial BG; longer acting, target fasting and postprandial BG	Fasting and postprandial BG
Hypoglycemia risk	Low	Low
Weight loss (kg)	2–5	1.5–3.0
Systolic blood pressure reduction (mmHg)	2–5	3–5
Cardiovascular outcomes	Unclear benefit in primary and secondary prevention	Reduction in CV death in patients with known ASCVD; unclear benefit in primary prevention
Potential adverse effects	Gastrointestinal upset, pancreatitis/pancreatic cancers, thyroid tumors/cancers, long-term safety not established	Genitourinary infections, diabetic ketoacidosis, bone fractures, long-term safety not established
Administration	Subcutaneous injections, twice daily to once weekly; may require reconstitution and use of prefilled pens	Oral, once daily
Cost/day (US $)[72]	13.56–21.37	12.10
Cost/QALY[a64–69]	EXEN BID vs IG: dominate to £30,000 EXEN QW vs IG: £9,400–£13,000	DAPA vs SITA: £6,800 DAPA vs MET: £2,700

SGLT-2 Inhibitors and GLP-1 Agonist are some of the efficacious 2nd line treatments for Type 2 DM. They have an added advantage of limited risk of hypoglycemia and positive or no effects on BP, Weight and Cardiovascular events. Some studies show that these are cost-effective 2nd line drugs. While selecting the drugs of treatment of type 2 DM one should keep in mind of the side effect profile, HBA1C reduction, cost, weight consideration , patient preferences and the comorbid conditions of the patient(8).

One of the most important question is what are the factors that should be taken into account to guide the choice between SGLT-2 inhibitors and GLP-1 Agonists (10).

In one of the metanalysis studies done to estimate the cardiovascular outcomes related to the use of GLP-1 agonist and SGLT-2 inhibitors with or without established Atherosclerotic cardiovascular disease (ASCVD). The primary outcomes of this study were Myocardial infarction, stroke, cardiovascular death, Hospitalization for heart failure and progression of kidney disease. The study showed that although both GLP-1 agonist and SGLT-2 inhibitors reduce the risk of cardiovascular event related death, in patients with known ASCVD, But neither reduces the risk in patients without established ASCVD. As compared to SGLT-2, Only GLP-1 Agonist reduces the risk of stroke. In contrast, SGLT-2 inhibitors are more effective in reducing the relative risk of hospitalization for heart failure (33% vs. 7%) (9,11).

2. METHODOLOGY

In this review article, the data is pooled from various types of literature referring the web to know at a glance about diabetes, its pathophysiology and treatment guidelines and to also know at a glance about the comparison b/w SGLT-2 and GLP-1 mortality benefits.

To understand the medical relevance of this study, we collected the information from the studies done I the past and made a relevant conclusion accordingly.

3. RESULTS AND CONCLUSIONS.

Type 2 DM is one of the most prevailing chronic disease worldwide. It is associated with a vast number of complications and has significant mortality and morbidity. Despite the availability of wide number of ant diabetic medications, a large population of patients land into both microvascular as wells as macrovascular complications.

Metformin remains the first line and most effective medication, yet it is not best to use as a single drug regime in most of the patients. Now a days the most effective treatment in Type 2DM is a combination of multiple oral hypoglycemic drugs depending on the underlying medical conditions of the patient. SGLT-2 Inhibitors and GLP-1 Agonist are some of the efficacious 2nd line treatments for Type 2 DM.

On reviewing the literature and the studies done in the past, It is estimated that Both GLP-1 Agonist and SGLT-2 Antagonist are beneficial in reducing the number of complications especially associated with cardiovascular outcomes. SGLT-2 Inhibitors are particularly more efficacious in preventing the cardiovascular risks and associated mortality as compared to GLP-1 agonist which is more advantageous in patients with chronic kinder disease.

Although, approximate conclusions can be made from the pooling of the data from the literature, a definitive conclusion can only be made with further research studies.

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