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Original Article

Tug of War: DPP4 Inhibitors vs SGLT2 Inhibitors

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ABSTRACT

More than 90% of persons with type 2 diabetes will require more than metformin monotherapy to meet their glucose targets. The sodium–glucose cotransporter 2 (SGLT2) and dipeptidyl peptidase-4 (DPP-4) inhibitor classes are among the several second-line treatments for type 2 diabetes glucose management. In comparison to prior classes, these newer classes provide a number of advantages, including a lower risk of hypoglycemia and weight gain, as well as no requirement for dose titration. An SGLT2 inhibitor can cause rapid, considerable, and long-term weight reduction (about 2–3 kg in 6 months) by causing glucose and consequently calorie loss in the urine as compared with DPP4 inhibitors which are weight neutral. Also SGLT-2Is have shown better reno and cardio protective effects as compared with DPP4 inhibitors but contraindicated in setting of CKD as against DPP4 inhibitors.

Conclusion: To conclude SGLT2 inhibitor may be beneficial in a younger person with suboptimal blood glucose management early in their illness course, weight loss is a focus, and bladder dysfunction and comorbidities are not limiting factors while in an older person for whom weight loss is not a priority and bladder dysfuncjh6tion and comorbidity are commonly limiting factors, a DPP-4 inhibitor with good tolerance and efficacy could be beneficial. Now'-days since combination pills are also available, they can be used for their complementary beneficial effects.

Key Words: *Tug of War; DPP4 Inhibitors; SGLT2 Inhibitors*

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INTRODUCTION

Multiple processes are involved in the aetiology of type 2 diabetes, including decreased insulin secretion, decreased insulin sensitivity, increased hepatic glucose production, impaired responses to incretin hormones, and increased renal reabsorption of glucose [1]. To effectively control hyperglycemia in people with type 2 diabetes, various interventions are frequently required. Combining anti-diabetic drugs with complementary modes of action may improve glucose-lowering effectiveness without jeopardising therapeutic safety [1, 2]. More than 90% of persons with type 2 diabetes will require more than metformin monotherapy to meet their glucose targets. Dual therapy may begin early in the course of their treatment, when it is obvious that metformin alone is insufficient (primary failure), or later as metformin's efficacy begins to decline (secondary failure) [3].

The sodium–glucose cotransporter 2 (SGLT2) and dipeptidyl peptidase-4 (DPP-4) inhibitor classes are among the several second-line treatments for type 2 diabetes glucose management. In comparison to prior classes, these newer classes provide a number of advantages, including a lower risk of hypoglycemia and weight gain, as well as no requirement for dose titration [4].

Before we delve deep into the question of better option for diabetes management, lets first understand the mechanism of action of both these drugs.

Mechanism of action of DPP4 inhibitors:

GLP-1 (glucagon-like peptide-1) is an incretin hormone that causes glucose-dependent insulin production, glucagon suppression, delayed stomach emptying, and a reduction in caloric intake, all of which are likely due to centrally controlled signalling [5, 6 & 7]. It is produced largely in intestinal L cells after posttranslational processing of proglucagon and is released in two forms: GLP-1(7, 36) and GLP-1(7, 36) (7, 37)

DPP-4 inhibitors, which inhibit the main enzyme responsible for the breakdown of endogenous GLP-1, are another family of pharmacotherapeutic drugs that employ the incretin system. GLP-1 clearance is reduced, resulting in an increase in active GLP-1 concentrations and a reduction in fasting and postprandial glucose levels [5]. Both active

incretin hormones, GLP-1 and glucose-dependent insulinotropic polypeptide, are increased by DPP-4 inhibitors (secreted by the enteroendocrine L and K cells, respectively, which are substrates for DPP-4). This leads to better -cell response to current glucose concentrations and glucagon secretion suppression [8]. The double-incretin receptor knockout (DIRKO) animal has shown unequivocally that incretin hormones cause these effects [9].

In addition to its primary incretin effect, DPP4 inhibitors have other actions as well viz:
1) DPP4 inhibitors are weight neutral.
2) They have varied beneficial effect on lipid profile with lowering of total cholesterol and LDL-C.

Mechanism of action of SGLT-2 inhibitors:

Gliflozins, also known as sodium-glucose co-transporter 2 or sodium-glucose linked transporter 2 (SGLT2-Is), are a relatively new class of oral medicines used to treat type 2 diabetes mellitus (T2DM). The blockage of SGLT2 channels in the renal proximal convoluted tubule, which is responsible for roughly 90% of filtered glucose reabsorption, is their mechanism of action [2, 10].

The renal threshold for glucose excretion is reduced by SGLT2-Is from roughly 10 mmol/L (180 mg/dL) to 2.2 mmol/L (40 mg/dL) [11]. Blood glucose levels are lowered as a result of the increased urine glucose clearance. This, like other anti-hyperglycemic medications, decreases glucotoxicity and enhances -cell activity and whole-body insulin sensitivity [12].

The other actions of SGLT2'-Is
1) They are weight negative, owing to calorie loss due to increased glucose excretion via urine. Though the sustainability of this effect is debatable.
2) They reduce Triglyceride levels and increase in HDL-C levels [13].
3) Its use may be associated with reduced rates of heart failure and cardiovascular death in people with established cardiovascular disease [14].

Let's now compare the drugs based on following parameters:

Efficacy:

When choosing between an SGLT2 and a DPP-4 inhibitor, the most obvious first question to ask is how efficiently each class lowers glucose. SGLT2 inhibitors have been shown in clinical studies to reduce HbA1c by 7.2 mmol/mol (0.66%; 95 percent confidence interval [CI], 0.73%, 0.58%; 15. 7.2 mmol/mol [0.69%] 95 percent CI, 0.79 percent, 0.61 percent; Liu et al. It has been determined that neither medication class achieves considerable glucose reduction in persons with type 2 diabetes, recent head-to-head studies suggest that SGLT2 inhibitors may have a better glucose-lowering effect than DPP-4 inhibitors [15, 16 & 17]. DPP-4 inhibitors may have a somewhat higher effect on fasting plasma glucose than SGLT2 inhibitors in combination with metformin, but the opposite may be true for post-prandial glucose levels [18]. In patients with renal impairment, DPP4 inhibitors have shown better results than SGLT'-2Is [19].

Weight loss is a significant component of type 2 diabetes therapy in overweight or obese patients, especially in early diabetes when weight loss is a high priority and can be difficult to attain, reinforce, or maintain. When glucose levels aren't properly controlled as they should be, it's typical to propose stepping up weight-loss efforts while simultaneously putting in additional glucose-lowering medications. It's vital to remember that several diabetic drugs (sulfonylureas, insulin, and thiazolidinediones) have the potential to promote weight gain, and hence will work against the advice to increase weight-loss lifestyle treatments. SGLT2 inhibitors are weight negative, whereas DPP-4 inhibitors are weight neutral.

An SGLT2 inhibitor can cause rapid, considerable, and long-term weight reduction (about 2–3 kg in 6 months) by causing glucose and consequently calorie loss in the urine. The majority of weight reduction caused by SGLT2 inhibition is fat loss, particularly visceral fat, which is advantageous to the waistline and overall wellness [20]. Surprisingly weight loss ends after 6 months of SGLT2 suppression, despite the fact that glycosuria remains.

Tolerance, safety and side effects:

DPP4 inhibitors have so far so far shown excellent tolerance in patients [21] with some risk of pancreatic cancer and slightly higher incidence of heart failure in patients on DPP4 inhibitors [22].

SGLT2 inhibitors block SGLT2 protein in proximal tubule responsible for 90% glucose reabsorption. Its efficacy largely depends on GFR. SGLT2 inhibitors on the other hand have side effects of excessive urination which settles down with time but may be inconvenient for those who are elderly, have bladder, pelvic floor or prostate problems, higher incidence of genital thrush especially in females, higher incidences of dizziness and fainting in those suffering from postural hypotension, though the diuresis caused is only mild to cause any symptoms in most of the cases [17, 19 & 23]. SGLT-2 inhibitors may not be safe in scenario of renal impairment [17].

Since the cardiovascular events account for maximum mortality and morbidity in patients suffering from DM, cardiovascular safety is a major concern in all anti-diabetic medications. Moreover, it is now mandatory for these drugs to undergo cardiovascular safety trials before getting a green signal. On these paramenters, SGLT-2 inhibitors have shown better record so far as compared with DPP-4 inhibitors, though the cardiovascular safety profile of DPP-4 are not in unacceptable range. However, SGLT-2 Is have shown favourable outcomes in terms of mortality when used in patients with CAD albeit the mechanism of action of these effects are yet unknown. One of the reasons could be favourable effects on lipid profile and reduction in visceral adipose tissue [24, 25].

Though both DPP-4 inhibitors and SGLT-2 inhibitors have shown reno-protective effects in different trials and slower decline in renal functions and or requirement of dialysis, in setting of CKD, which is a major complication of DM, use of SGLT_2 inhibitors is not recommended, unlike DPP-4 inhibitors [25, 26, 27 & 28].

DPP-4 inhibitors with their growth promoting action can have deleterious effect on medullary carcinoma of thyroid (MCT) and thus are contraindicated in MCT and multiple endocrine noeoplasia. Though large clinical trials have failed to show higher risk of pancreatic cancer, history of pancreatitis or pancreatic cancer is a contraindication for the use of DPP4 inhibitors [29, 30 & 31].

SGLT-2 inhibitors increase the production of ketone bodies by liver to compensate for the loss of glucose in urine, hence setting a pro-ketosis stage. In scenarios of excessive alcohol intake, stressful conditions like prolonged fasting or type 1 diabetes, SGLT-2Is use can potentiate development of ketoacidosis, hence contraindicated in type-1 diabetic patients. Thus any condition warranting stoppage of metformin will also contraindicate use of SGLT-2 Is [4, 32].

Other Considerations

Compliance with the patients is better with both the drugs. Single dosage per day for both category of drugs, lower chances of hypoglycaemia make it convenient for the patients for compliance in both the categories of drug. However price of both these classes of drugs are area of concern and one of the limiting factors for their rampant use inspite of favourable drug profile particularly in developing countries like India.

CONCLUSION

Looking at the profile of both the drugs a SGLT2 inhibitor may be beneficial in a younger person with suboptimal blood glucose management early in their illness course, weight loss is a focus, and bladder dysfunction and comorbidities are not limiting factors while in an older person for whom weight loss is not a priority and bladder dysfuncjh6tion and comorbidity are commonly limiting factors, a DPP-4 inhibitor with good tolerance and efficacy could be beneficial. Now'-days since combination pills are also available, they can be used for their complementary beneficial effects.

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