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COMPARISON BETWEEN THE EFFICACY OF SGLT2 INHIBITORS VERSUS DPP4 INHIBITORS IN INDIAN POPULATION: A SYSTEMATIC REVIEW

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Abstract

Introduction: India is among the nations with the largest number of individuals having Diabetes Mellitus. Various elements liable for the increasing magnitude of type 2 diabetes include pathophysiologic and hereditary components as well as the 'Asian Indian phenotype', which makes these patients more prone to acquire T2DM in comparison to Caucasians. In this review efficacy and safety of dipeptidyl peptidase-IV inhibitors and sodium glucose transport inhibitor is going to be reviewed and compared with each other to ascertain effective and safe treatment options across the spectrum of T2DM patients in India.

Material and Methods: 'Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) 2015 guidelines' were followed to report this systematic review with the inclusion of studies related to the use of oral hypoglycemic agents in Indian patients with type 2 Diabetes Mellitus and comparison between SGL2I and DPP4I in terms of efficacy, adverse effects, and other parameters. The search will be restricted to studies published in the English language on PubMed, Google Scholar, and the Indian Journal of Endocrinology and Metabolism (IJEM) from 2010 to 2021.

Results: The analysis of a number of studies revealed superiority of SGLT2I in several different parameters including reduction in HbA1c levels, improved glycemic control on follow up as well as positive effects on body weight and SBP reduction in comparison to the use of DPP4I. Moreover, use of SGLT2I showed improvement in the levels of TG and HDL-C values with modest worsening of LDL-C values. Reduction in fasting and postprandial glucagon levels was seen with the use of DPP4I in comparison to SGLT-2 inhibition resulting in more rapid insulin secretion and higher levels of intact incretin hormones. DPP4-I show a safe CV profile, however, the use of SGLT2-I resulted in better CV outcome and survival in DM patients as it significantly reduced the risk of all-cause death, CV death, MI and HF without any effect on stroke events. Adverse effects reported with the use of SGLT21 showed an increased risk of developing genital infection and in certain cases increased risk of amputations though not statistically significant. Although, DPP-4 inhibitors

(gliptins) showed some positive cardiac and vascular effects in preliminary studies, an unexpected higher risk of hospitalization for heart failure was reported with saxagliptin. **Conclusion:** Overall, SGLT2I showed more efficacy than DPP4I and revealed superiority in several different parameters making it a more suitable option to improve health outcomes in Indian Diabetic patients.

Keywords: Type 2 Diabetes Mellitus, SGL2I, gliflozins, DPP4I, gliptins, Antidiabetic Agents, Indian population, Indians, India, Asians, SGLT2 Inhibitors versus DPP4 inhibitors

Introduction:

Type 2 diabetes mellitus' is perhaps the most widely recognized type of non-transmittable and diverse disease, emerging as one of the major health related issue of the 21st century across the world. As a consequence of medical care crisis worldwide due to Type 2 diabetes mellitus, there is an expectation of roughly 300 million people getting affected by it by 2025. [1,2,3,4]

India is among the nations with the largest number of individuals having Diabetes Mellitus. In 2025 it is expected to become the diabetes capital of the world with an expected 80 million people effected with the disease.[2, 4] According to the current status, India is already depicting a large number of individuals affected by diabetes (roughly 73 million) demonstrating the fact that every fifth individual diagnosed with diabetes across the globe belongs from India. Approximately 50.9 million population of India is already experience ailing impacts of diabetes. In 2006, there were about 40.9 million Indian inhabitants with diabetes, out of which 90% were due to type 2 diabetes with fluctuating predominance in rural (2.4%) and metropolitan (11.6%) areas.[2]

The hazard of developing type 2 diabetes ascends with increasing age and hence, dominance of it is analyzed in the middle and older aged patients. Nonetheless, as of late its frequency is discovered to be escalating among younger generation as well.[2, 5, 6] This is particularly valid for low-and middle income nations where diabetes is reported to occur at a much early age in comparison to a more well developed countries.[7] In a cross country study, the age-explicit predominance of diabetes in youthful grown-ups between 30-34 years was 4% in males 3% in females.[6, 8]

Although, increase number of cases are reported in a younger generation, extensive contrast is seen in the etiology of diabetes in various parts of the world. While T1DM is a more common cause of early onset of Diabetes Mellitus in Caucasians of European descent, T2DM structures the major subtype in a few Asian nations. Etiological heterogeneity has been accounted as a cause of early stage diabetes in various districts of India.[6, 9]

Various elements liable for the increasing magnitude of type 2 diabetes include pathophysiologic and hereditary components as well as the 'Asian Indian phenotype', which makes these patients more prone to acquire T2DM in comparison to Caucasians.[1] Other factors consist of visceral abdominal obesity, lower beta cell capacity, and psycho-social factors such as undesirable eating regimens, inadequate adherence to medications, stationary ways of life, quick urbanization, morbid obesity and hereditary predisposition.[6, 10, 11] The fast change in the Indian economy is another major component behind the expansion in the pervasiveness of Diabetes Mellitus.[12]

The underlying pathology responsible for the development of Diabetes is the resistance to the insulin and gradual decrease in the production of sufficient amounts of insulin by the pancreas.[6] Due to the impaired function of insulin patients with type 2 diabetes can develop clinical features such as polyuria, polyphagia, polydipsia, impaired vision, lethargy and impaired healing of wounds. In India many patients recognize their symptoms in later stages when they have developed microvascular or macrovascular complications as a result of persistent hyperglycemia and metabolic anomalies due to the lack of awareness regarding it.[6, 12]

These patients with type 2 diabetes mellitus (T2DM) complications have a 2- to 3-fold increase likelihood of developing Cardiovascular disease (CVD).[13] About 40% of mortalities in patients with T2DM are ascribed to CVD. Likewise, there is a high occurrence of non-fatal cardiovascular (CV) occasions in patients with T2DM, with heart failure (HF) hospitalizations representing up to 33% of non-fatal CV occasions.[14]

Increase in the rate of diabetic cases in different age groups, mortality and complications associated with Diabetes along with the negative impact and stress on economy necessitates exploration and administration of efficacious drugs in India. Standard treatment regimen for the management of type 2 diabetes mellitus (T2DM) involves administration of metformin, sulfonylureas, meglitinides, thiazolidinediones, or insulin. Newer therapies, such as dipeptidyl peptidase-IV inhibitors and sodium glucose transport inhibitor are popular options that can be considered for the treatment of type 2 diabetes. In this review efficacy and safety of dipeptidyl peptidase-IV inhibitors and sodium glucose transport inhibitor is going to be reviewed and compared with each other to ascertain effective and safe treatment options across the spectrum of T2DM patients in India.

Systolic Blood Pressure: A post-hoc analysis from a randomized, double-blind, 24-week clinical trial of patients with type 2 diabetes (T2D) inadequately controlled with metformin showed SBP reduction of ≥ 2 mmHg in patients receiving dapagliflozin in comparison to saxagliptin as shown in table 2 (16) **.** Another study involving patients with T2DM on metformin plus sulfonylurea, demonstrated BP measurement less than 140/90 mm Hg or 130/80 mm Hg in patients receiving 300 mg canagliflozin versus 100 mg sitagliptin after 52 weeks.[23] Similarly, a retrospective study covering up to 30 months after CANA approval (March 2013) conducted on a total of 10,702 CANA and 17,679 DPP-4 patients showed that CANA patients were more likely to reach a systolic BP < 140 mmHg (HR = 1.07, P = 0.04, KM rates: 87.8% vs. 83.9%). but not a diastolic BP < 90 mmHg (HR = 0.95, P = 0.361), compared to DPP-4 patients.[18] Overall, these studies have demonstrated beneficial effects of SGLT2I on the values of blood pressure.

Lipid: An observational retrospective medical record review of 228 patients with type 2 diabetes, aged 25–65 years receiving a DPP-4I or SGLT2I as an add-on therapy to metformin and/or a sulfonylurea was carried out to look at the effects on lipid profile after 24 weeks of treatment by making use of analysis of covariance (ANCOVA). Results showed that using SGLT2I increases HDL-cholesterol (HDL-C) levels by 5.1 (95% CI, 3.0 to 7.1) mg/dl (p = 0.001) in comparison to 0.5 increase (95% CI, -0.9 to 2.0) mg/dl with a DPP-4I. However, SGLT2I also resulted in an increase in the levels of LDL-cholesterol (LDL-C) levels by 1.3 (95% CI, -5.1 to 7.6) mg/dl which were reduced by 8.4 (95% CI, -14.0 to -2.8) mg/dl with the help of a DPP-4 I (p = 0.046). No significant change was noticed in the levels of apolipoprotein A (p = 0.726), apolipoprotein B (p = 0.660), total cholesterol (TC) (p = 0.836), triglyceride (TG) (p = 0.867), and lipoprotein (a) (p = 0.991) between the DPP-4 I and the SGLT2I. According to this study, SGLT2I may be preferred as an add-on to metformin and/or a sulfonylurea in patients with low HDL-C for better outcomes in patients with CVD.[26, 27, 28, 29]
Another systematic review was carried out on Asian patients with type 2 diabetes mellitus to look at the effects of SGLT2is on lipid profiles in these patients. Similar findings were seen with improvement in the levels of TG and HDL-C values, but modest worsening of LDL-C values with the use of SGLT2is in comparison to a placebo. However, more evidence is needed to support these findings related to the effects of SGLT2is on lipid profiles.[30]

Glucagon: A single-center, randomized study conducted on 28 metformin-treated patients with type 2 diabetes (T2D) for 2 weeks showed that patients who were treated with 50 mg vildagliptin resulted in 15% lower fasting glucagon (35.6 ± 2.5 vs 39.4 ± 3.4 pmoL/L; P = .032) and postprandial glucagon levels (32.1 ± 2.3 vs 37.5 ± 2.7 nmoL/L min; P = .001) compared to SGLT-2 inhibition with 10 mg once daily dapagliflozin.

Material and Methods: Study design: 'Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) 2015 guidelines' were followed to report this systematic review. Studies related to the use of oral hypoglycaemic agents in Indian patients with type 2 Diabetes Mellitus and comparison between SGL2I and DPP4I in terms of efficacy, adverse effects,

and other parameters will be included. The search will be restricted to studies published in the English language and will be limited to studies published from 2010 to 2021.

Participants: Our systematic review is going to focus on Individuals 18 years old or above with an established diagnosis of type 2 diabetes mellitus confirmed by investigations. The patient population is going to be limited to the country of India in the majority of cases and will include diabetic cases with and without complications regardless of the duration of diabetes. Exclusion criteria will include patients who have type 1 diabetes mellitus or are diagnosed with gestational diabetes, or any other severe or chronic communicable diseases such as tuberculosis, Hepatitis B/C, and human immunodeficiency virus (HIV). In the case of research conducted outside of India, we will prefer studies reporting the effects of hypoglycemic drugs in Indians. However, in certain cases, studies that directly compare the effects of SGL2I versus DPP4i in diabetic patients other than Indians may also be reviewed to look at the possibility of its efficacy and applicability in the Indian population.

Outcomes: The primary outcome is to identify and compare the effect of oral hypoglycemic drugs such as SGL2I and DPP4I on the glycemic index in individuals living in India with type 2 diabetes mellitus.

Search strategy: We did an extensive electronic database search on PubMed, Google Scholar, and the Indian Journal of Endocrinology and Metabolism (IJEM). The initial search was conducted on PubMed followed by customized research on the other databases mentioned. Duplicates will be eliminated by exporting the studies to an Excel spreadsheet for screening. The search date for studies reviewed on Pubmed was 1st June 2021 and for Google Scholar and IJEM was 5th June 2021. The search concepts with their respective keywords are mentioned below in table 1.

Table 1 : Search concepts and key terms

Population	Diabetes Mellitus, T2DM, type-2 diabetes, Indian population, Indians, Asia
Intervention	SGL2I, gliflozins, DPP4I, gliptins, Antidiabetic Agents
Combined keywords	Type 2 DM in Indians, Sgl2i in Indian population, Sgl2i in Indians, Sgl2i in Asians, DPP4 inhibitors in Indian population, DPP4 inhibitors in Indians, SGLT2 Inhibitors versus DPP4 inhibitors

Results:

Table 2: Comparison between the effects of SGLT2 I vs DPP4 I on different metabolic parameters in different studies.

Type of study	Intervention	Hba1c	FPG	Weight	Systolic BP	Result
RCT- 52 weeks trial (15) A	Canagliflozin 300 mg (n=377) vs sitagliptin 100 mg (n=378)	-1.03% [-11.3 mmol/mol] vs -0.66% [-7.2 mmol/mol] reduction	[-1.3 mmol] (P < 0.001) for SGLT2I		−5.1 vs 0.9 mmHg (P < 0.001)	Greater reduction in all parameters with cangliflozin
Double-blind, randomized, 24-week clinical trial (16) B	Dapagliflozin 10 mg (n = 179) vs saxagliptin 5 mg (n = 176)	-0.32% [-0.54, -0.10]; p < 0.005) [95% CI] for Dapa	(-0.98 [-1.42, -0.54] mmol/L; p < 0.0001) for Dapa	(-2.39 [-3.08, -1.71] kg; p < 0.0001) for Dapa	(-3.89 [-6.15, -1.63] mmHg; p < 0.001) for Dapa	Endpoint composite reduction with dapagliflozin treated patients was greater than saxagliptin for all parameters.
Review of 25 randomized trials, which involved 14 619 patients (17) C	SGLT-2is vs DPP-4is	0.04%-0.22%, P = .005, 95% credible interval [CI],) for SGLT-2is	0.58-1.01 mmol/L, P < .00001, 95% CI) for SGLT-2is			SGLT-2is plus Met was associated with a more significant decrease in FPG than was DPP-4is plus Met.
Retrospective	CANA 100mg	HbA1c < 7%		BW loss ≥	Systolic BP <	CANA more

observational study (18) E	(N=10,702) vs DPP-4 agent (N=17,679)	more likely in patients on CANA than DPP-4 (hazard ratio [HR] = 1.10, P = 0.007)		5% in CANA vs DPP-4(HR = 1.46, P < 0.001,	140 mmHg (HR = 1.07, P = 0.04, compared to DPP-4 patients.	likely to decrease HbA1c, systolic BP, and weight loss than DPP-4 inhibitors
Observational Prospective Cohort Study (19) F	Canagliflozin (N = 1472) vs sitagliptin (N = 1472)	(-0.93% versus -0.57%, respectively; p = 0.004)				Patients on canagliflozin had greater reductions in HbA_{1c} than patients on the sitagliptin
Control cohort study (20) EE	CANA (n = 729) vs DPP-4 inhibitor (n = 710)	(-0.92% vs. -0.63% respectively, p < 0.001)				CANA use associated with greater HbA1c reduction in comparison to DPP-4 inhibitors

Discussion: In this systematic review, we looked at several different types of studies conducted around the globe that did a comparison of SGLT2I with DPP-4 inhibitors in terms of its efficacy on following metabolic parameters and adverse effects with an intention to get a better analysis regarding the more effective drug usage in Indian population.

HbA1C: The majority of the studies have shown beneficial effects of SGLT2I on the reduction of HbA1c levels in comparison to the use of DPP4I (15, 16, 17, 18, 19, 20-Table 2). Several cohort studies were also conducted to look at the glycemic control on follow up. One study during follow-up demonstrated that HbA1c of <8% (66.0% vs. 58.6%, p = 0.004) and <7% (35.4% vs. 29.9%, p = 0.022) were achieved at a higher rate in CANA cohort relative to the DPP-4 inhibitor cohort.[20]
Similarly, a post hoc analysis compared the durability of these effects over a short- and long-term follow-up (24 and 102 weeks respectively) in patients with T2DM who were inadequately controlled with metformin (≥1500 mg/day). These patients were either receiving dapagliflozin (10 mg/day) or saxagliptin (5 mg/day). A low coefficient of failure [CoF]) CoF value indicated greater durability and it was lower for dapagliflozin versus saxagliptin over 18-24 weeks (-1.38%/year; 95% CI, -2.41 to -0.35; P = .009) and 20-102 weeks (-0.37%/year; 95% CI, -0.73 to -0.02; P = .04).[21] Another study also showed that CANA patients were more likely to reach and maintain HbA1c below threshold versus SITA patients suggesting more durable glycemic control with CANA.[22]

Weight: Several studies have shown positive effects of SGLT2I on body weight reduction in comparison to the use of DPP4I.[15, 16, 18, 24, 25] As shown in table 2[16], more patients treated with dapagliflozin in comparison to saxagliptin achieved the composite endpoint of weight loss ≥ 2 kg. Similarly, weight loss of ≥ 5% (HR = 1.46, P < 0.001, KM rates: 55.2% vs. 46.2%), was reported in one study with the use of SGLT2I in comparison to the patients using DPP-4[18] and greater than 10 lb (4.5 kg) weight loss from baseline, and a BMI less than 30 kg/m² at week 52, with canagliflozin versus sitagliptin in another study.[23, 24, 25]

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Effects on heart: A meta-analysis on randomized trials on more than 200 patients was done to evaluate the effects of DPP4-I and SGLT2-I on all-cause and CV mortality, stroke, new onset of heart failure (HF), and myocardial infarction (MI). According to the results, DPP4-I show a safe CV profile as they do not affect all-cause (RR: 1.010; 95% CI: 0.935-1.091) and CV (RR: 0.975; CI: 0.887-1.073) mortality as well as the risk of MI (RR: 0.915; CI: 0.835-1.002), stroke (RR: 0.933; CI: 0.820-1.062) and HF (RR: 1.083; CI: 0.973-1.205) in patients with type 2 DM. However, the use of SGLT2-I resulted in better CV outcome and survival in DM patients as it significantly reduced the risk of all-cause death by 28% (RR: 0.718; CI: 0.613-0.840), CV death by 33% (RR: 0.668; CI: 0.544-0.821), MI by 20% (RR: 0.803; CI: 0.668-0.965) and HF by 35% (RR: 0.652; CI: 0.517-0.823) without any effect on stroke (RR: 1.158; CI: 0.912-1.469) events.[33]
Another review was done to look at the CV effects of new oral glucose-lowering agents. Two CV outcome trials in type 2 diabetes mellitus patients showed remarkable positive results with the use of SGLT-2 inhibitors (gliflozins). Empagliflozin in EMPA-REG-OUTCOME reduced major cardiovascular events, all-cause mortality, CV mortality and hospitalization for heart failure. However, In the CANVAS trial, canagliflozin failed to reach a statistically significant reduction in CV mortality. DPP-4 inhibitors (gliptins) resulted in some positive cardiac and vascular effects in

prior studies. However, an unexpected higher risk of hospitalization for heart failure was reported with saxagliptin.[34]

Another retrospective, observational, single-center study of 89 patients with ASCVD or HF with a mean follow-up period of 2 years was analyzed regarding the effect of SGLT2I and DPP4I. N-terminal prohormone of brain natriuretic peptide (NT-pro BNP) and 2-D echocardiography were used to assess cardiovascular function. Results showed that SGLT2I improves cardiovascular function in T2DM with coronary artery disease in comparison to DPP4I.[35]

Another study showed that sitagliptin was significantly more effective than dapagliflozin at improving cardiometabolic risk factors, making SGLT2I more suitable than DPP-4I for preventing cardiovascular events in patients with early-stage but inadequately controlled type 2 diabetes.[36]

Moreover, in an observational cohort study SGLT2I was associated with lower risk of cardiorenal disease, HF, CKD, all-cause and cardiovascular mortality; HR (95% confidence interval), 0.56 (0.42-0.74), 0.71 (0.59-0.86), 0.44 (0.28-0.69), 0.67 (0.59-0.77), and 0.61 (0.44-0.85), respectively in comparison to DDP4I. No differences were observed for stroke [0.87 (0.69-1.09)] and MI [0.94 (0.80-1.11)].[37] Evidence of another study showed that a total of 29 916 adults prescribed an SGLT2I compared with 29 916 adults prescribed a DPP-4I had low events of hospitalization due to heart failure or death, and a decrease rate of hypoglycemia, but a higher rate of diabetic ketoacidosis.[38]

Overall, the majority of studies have demonstrated the beneficial effects of SGLT2I on cardiovascular health in comparison to DPP4I.

Adverse effects:

A new user cohort study using data from the Truven Health Market Scan (2009-2015) databases was conducted on patients aged ≥18 years to determine the risk of amputations associated with SGLT2I relative to DPP4I with 30216 comparable patients in each group after matching. Over a median follow-up of 0.6 years, there were 60 amputations (SGLT2i: 36; DPP4i: 24), most at the level of the partial foot (75%) and associated with diabetes-related vascular disease (66.7%). The incidence of amputations was more in patients receiving SGLT2I (1.62 vs. 1.15/1000 person) with a HR of 1.38 (CI: 0.83-2.31). All SGLT2i had an elevated, though not statistically significant, the risk for amputations.[39]

In another recent meta-analysis of randomized controlled trials of SGLT2I in patients with diabetes positive association was seen between SGLT2I and the risk of lower limb events. These results support the potential mechanism of a volume depletion effect of SGLT2i as a cause of the increased risk of amputations. Therefore, medications that induce a contraction of plasma volume should be introduced cautiously in patients with diabetes at high risk of diabetic foot amputation.[40, 41, 42, 43]

Another 52-week, randomized, double-blind, phase 3 study with subjects using stable metformin plus sulfonylurea (N = 755) were given 300 mg canagliflozin or 100 mg sitagliptin everyday. Overall adverse events rates were similar with canagliflozin (76.7%) and sitagliptin (77.5%). Higher incidences of genital mycotic infections and osmotic diuresis-related side effects were seen in patients receiving canagliflozin, which led to discontinuation in one case. Hypoglycemia rates were similar in both groups.[15] Other studies also showed an increased risk of developing genital infection with the use of dapagliflozin in comparison to saxagliptin.[16, 44, 45, 46]

Additionally, an unexpected higher risk of hospitalization for heart failure was reported with saxagliptin. Although, DPP-4 inhibitors (gliptins) showed some positive cardiac and vascular effects in preliminary studies. However, subsequent CV outcome trials with alogliptin, saxagliptin, and sitagliptin failed to exhibit any superiority in comparison to placebo in patients with type 2 diabetes mellitus and high CV risk.[34, 47, 48, 49]

A longitudinal cohort of diabetic patients was also conducted to evaluate the risk of developing new-onset AF with the use of SGLT2i compared to DPP4i Subgroup analysis showed that the use of SGLT2i was associated with a lower risk of new-onset AF compared with DPP4i in real-world

practice across several subgroups including old age, females, patients with cardiovascular disease, hemoglobin A1c 8%, and chronic kidney disease.[50]

Conclusion:

The analysis of a number of studies doing a comparison of SGLT2I with DPP-4 inhibitors revealed superiority of SGLT2I in several different parameters including reduction in HbA1c levels, improved glycemic control on follow up as well as positive effects on body weight and SBP reduction in comparison to the use of DPP4I. Moreover, use of SGLT2I showed improvement in the levels of TG and HDL-C values with modest worsening of LDL-C values. Reduction in fasting and postprandial glucagon levels was seen with the use of DPP4I in comparison to SGLT-2 inhibition resulting in more rapid insulin secretion and higher levels of intact incretin hormones. DPP4-I show a safe CV profile, however, the use of SGLT2-I resulted in better CV outcome and survival in DM patients as it significantly reduced the risk of all-cause death, CV death, MI and HF without any effect on stroke events.

Adverse effects reported with the use of SGLT21 showed an increased risk of developing genital infection and in certain cases increased risk of amputations though not statistically significant. Although, DPP-4 inhibitors (gliptins) showed some positive cardiac and vascular effects in preliminary studies, an unexpected higher risk of hospitalization for heart failure was reported with saxagliptin. Overall, SGLT2I showed more efficacy than DPP4I and therefore could be considered as an option to improve health outcomes in Indian Diabetic patients.

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