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Original Research Article

Need of the hour: pharmacovigilance study of SGLT-2 inhibitors

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ABSTRACT

Background: Diabetes mellitus represents a global pandemic. Various pharmacotherapy and non-pharmacotherapy measures are advocated for its control. The latest in the pharmacotherapy are Sodium Glucose Transporter -2 (SGLT-2) inhibitors, widely used. Many studies suggest adverse effects related to SGLT-2 inhibitors, evidence still not conclusive and few data from India. Hence this study was planned.
Methods: Cross-sectional study over a period of 02 months, recorded demographic details and history of various adverse drug reactions reported with the use of SGLT-2 inhibitors.
Results: Majority of the study participants were females (58%) and belonged to the age group of 40-70 yrs. Urinary tract infections (UTI) and genital infections was more seen in the users of dapagliflozin, followed by empagliflozin and canagliflozin.
Conclusions: SGLT-2 Inhibitors offer a unique therapeutic approach to the management of Diabetes Mellitus. Further evaluation of the safety profile and the risk-benefit analysis is the need of the hour.

Keywords: Diabetes mellitus, Genital infections, Pharmacovigilance, Safety profile, SGLT-2 Inhibitors, UTI

INTRODUCTION

Diabetes mellitus is a chronic metabolic disorder with association of elevated blood glucose levels resulting from either insulin deficiency or action. It represents a global pandemic with the number of affected individuals getting quadrupled over the last three decades.[1-3] An estimate suggests that more than 415 million are affected by diabetes globally with numbers expected to cross 640 million by 2040.[1-4] It is projected that globally 1 in every 11 adults are diabetic, with 90% of affected individuals are of type 2 diabetes mellitus.[3,4] Initially considered to be a disease of affluent countries, latest report by International Diabetic Federation (IDF) suggests that China (109.6 million) and India (69.2 million) represent the countries with largest number of diabetics.[1-4]

In India the overall prevalence stands at 7.3%, with a higher prevalence in urban areas compared to rural areas and a higher prevalence in states with high per-capita GDP.[5] In collaboration with genetic predisposition, unhealthy dietary habits and lifestyle contribute to an individual susceptibility to diabetes.[3,5] The long term complications of uncontrolled hyperglycaemia predominantly involve the vasculature contributing to microvascular and macrovascular changes affecting various organs.[6] It is estimated that globally around 193 million diabetics escape the radar of diagnosis contributing to the long term complications.[6]

Management of diabetes includes lifestyle modifications along with pharmacotherapy. The approved pharmacotherapy includes various formulations of insulin (short acting, intermediate acting and long acting), biguanides, thiazolidinediones, sulfonylureas, meglitinide

analogues, dipeptidyl peptidase-4 (DPP-4) inhibitors, Sodium glucose co-transporter-2 (SGLT-2) inhibitors and alpha-glucosidase inhibitors.[7,8] Biguanide like metformin act by inhibiting the mitochondrial respiratory chain complex leading to an increase in ratio of adenosine monophosphate (AMP) to adenosine di-phosphate (ADP). This further activates AMP-activated protein kinase (AMPK) which ultimately inhibits gluconeogenesis. Metformin also inhibits glycerol-3-phosphate dehydrogenase in mitochondria inhibiting gluconeogenesis.[9]

Sulfonylureas like glimepiride, glipizide and glyburide acts by binding to ATP-dependent sulfonylurea receptor leading to stimulation of insulin secretion from pancreatic beta cells.[10] Thiazolidinediones (pioglitazone) act as agonist at peroxisomal proliferative activated receptor-alpha (PPAR-α) and leads to insulin sensitizing effect.[11] Meglitinide analogues (repaglinide and nateglinide) also are insulin secretagogues, but are shorter and faster acting.[12] DPP-4 inhibitors prevent the breakdown of glucagon like peptide-1 (GLP-1) secreted by intestinal tract, which inhibits glucagon release, gluconeogenesis and gastric emptying gets delayed.[13]

There has been a better understanding of kidney's role in glucose homeostasis leading to development of SGLT-2 inhibitors. SGLT-2 inhibitors decrease renal glucose reabsorption, excretion and subsequent reductions in plasma glucose which results in enhanced urinary glucose and glycosylated haemoglobin concentrations.[14] The novelty of action gives SGLT-2 inhibitors the added advantage of combining with other glucose-lowering agents.[14] SGLT-2 inhibitors are known to reduce body weight, blood pressure and serum uric acid. Three drugs, namely dapagliflozin, empagliflozin and canagliflozin have been recently introduced in India.[15,16]

SGLT-2 inhibitors although considered to be well tolerated, potential adverse effects of urinary tract infections and mycotic genital tract infections exists due to continuous presence of urinary glucose.[17] By increasing renal tubular reabsorption of phosphate and parathyroid hormone secretion SGLT-2 inhibitors increase FGF-23 secretion from osteocytes which causes bone resorption leading to fractures. As SGLT2 inhibitors cause a modest osmotic diuresis, there may be a risk of hypotension, hypovolemia, and dehydration.[18]

Although few studies have been conducted on the adverse effects noted with this new class of anti-diabetic drugs, there is a paucity of data on the effects associated with the use of these agents in Indian population. Hence this study was conducted to report the adverse effects associated with the use of SGLT-2 inhibitors.

Aim and objective was to study the adverse events associated with the use of SGLT-2 inhibitors (empagliflozin, dapagliflozin and canagliflozin) in Indian patients of type 2 diabetes mellitus.

METHODS

It was a cross-sectional study conducted in the endocrinology department of a 1000 bedded tertiary care hospital. After obtaining approval from institutional ethical committee the study was conducted on 100 randomly selected diabetic patients aged >18 years, of either sex, providing informed consent and receiving one of the SGLT-2 inhibitors as treatment. Those patients declining the informed consent and pregnant women were excluded from the study. The study was conducted over a period of 02 months in the months of May and June 2018.

The demographic profile (age, gender and locality) of those participating in the study was recorded. The duration from the onset of diabetes and their treatment regimen was recorded. Any history of any adverse reactions during the use of SGLT-2 inhibitors (Urinary tract infections; genital infections; symptoms of hypoglycaemia-dizziness, fainting; increased urine frequency/ volume; symptoms suggestive of DVT-Pain in the legs, redness, swelling; history of fractures, stroke and any other adverse effects other than above) was recorded. All the data were tabulated and analyzed. The causality assessment of adverse reactions reported was done using WHO-UMC criteria.

RESULTS

Majority of the study participants were females (58%) and belonged to the age group of 40-70 yrs (Table 1). Out of 100 individuals recruited into the study majority of them were prescribed canagliflozin (54%) followed by empagliflozin (33%) and dapagliflozin (13%). The users of dapagliflozin reported more history of UTI (76.92%) in comparison to empagliflozin (39.4%) and canagliflozin (31.48%). Similar to UTI, genital infections were more with dapagliflozin (76.92%). The users of empagliflozin did not report any symptoms of DVT, whereas it was reported by users of canagliflozin (18.52%) and dapagliflozin (23.08%) (Table 2, Figure 1).

Table 1: Demographic characteristics.

Demographic characteristics		
Gender	Males	42
	Females	58
Age (In yrs)	1-10	Nil
	11-20	Nil
	21-30	Nil
	31-40	12
	41-50	21
	51-60	25
	61-70	29
	71-80	13
	81-90	00
	91-100	00

Table 2: History of adverse reactions reported by users of SGLT-2 inhibitors.

H/O adverse reactions on SGLT-2 inhibitors	Canagliflozin (54)		Empagliflozin (33)		Dapagliflozin (13)	
	Reported	Not reported	Reported	Not reported	Reported	Not reported
Urinary tract infections	17(31.48%)	37 (68.52%)	13 (39.4%)	20 (60.6%)	10 (76.92%)	03 (23.08%)
Genital infections	17 (31.48%)	37 (74.08%)	14(42.42%)	19(57.58%)	10 (76.92%)	03 (23.08%)
Symptoms of hypoglycemia: dizziness, fainting	27 (50%)	27 (50%)	13 (39.4%)	20 (60.6%)	03 (23.08%)	10 (76.92%)
Increased urine frequency/volume	04 (7.41%)	50 (92.59%)	10 (30.31%)	23 (69.69%)	03 (23.08%)	10 (76.92%)
Symptoms suggestive of DVT (Pain in the legs, redness, swelling)	10 (18.52%)	44 (81.48%)	Nil	Nil	03 (23.08%)	10 (76.92%)
History of fractures	04 (7.41%)	50 (92.59%)	Nil	33 (100%)	Nil	13 (100%)
History of stroke	Nil	54 (100%)	1 (3.03%)	32 (96.97%)	Nil	13 (100%)

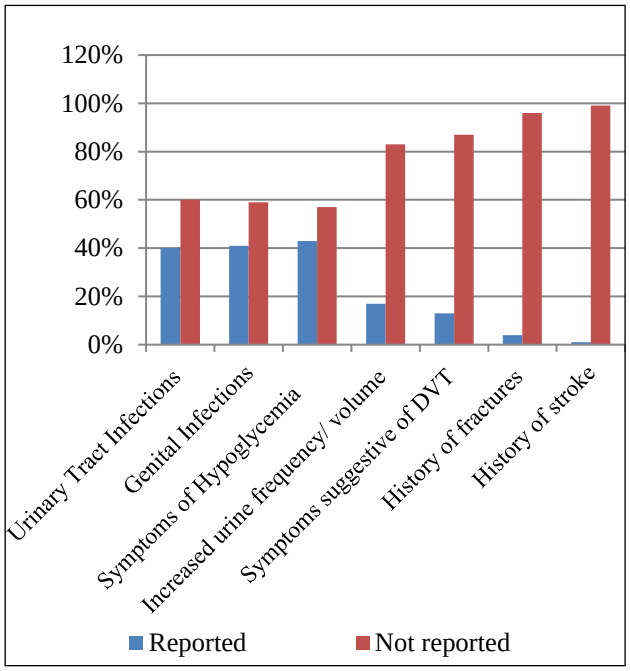

Figure 1: Summary of adverse reactions reported by users of SGLT-2 inhibitors.

History of fractures was reported by only the users of canagliflozin (7.41%). There was only one participant who reported a history of stroke 06 months ago. Amongst the other adverse effects reported include nausea (9%), vomiting (3%), dry mouth (2%), anorexia (2%) and hair loss (1%) (Table 2).

According to WHO-UMC scale, the casuality assessment of adverse drug reactions (ADRs) reported by users of SGLT-2 inhibitors revealed, 95% ADRs as possible and the remaining 5% ADRs as unclassifiable (Figure 2).

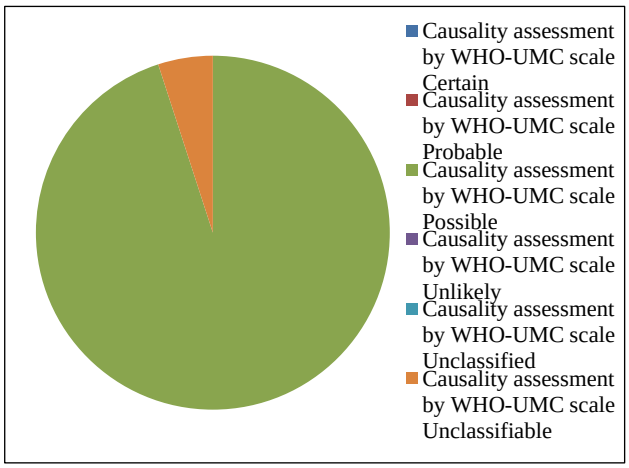

Figure 2: Adverse drug reactions.

DISCUSSION

Pharmacotherapy of diabetes is an ever evolving arena with only insulin, metformin and pioglitazone ruling the zone initially, but off late new groups of drugs DPP-4 inhibitors (gliptins) and SGLT-2 inhibitors are often used as add on drugs. Hence, this study was planned to assess the prevalence of adverse effects in users of SGLT-2 inhibitors.

In our study the users of dapagliflozin reported highest incidence of UTI (76.92%) followed by canagliflozin and empagliflozin. The results were in line with meta-analysis of randomized controlled trials (RCTs) on SGLT-2 inhibitors safety and efficacy by Liu XY et al. The meta-analysis clearly highlighted the increased risk of UTIs in users of SGLT-2 inhibitors in comparison to placebo.[19] However; this was refuted by Ueda P et al, in their nationwide registry based cohort study assessing the use of SGLT-2 inhibitors and risk of serious adverse events.

They reported that SGLT-2 inhibitors in comparison to GLP-1 receptor agonists were not associated risk of serious UTIs.[19] Liu J et al, in their systemic review and meta-analysis of randomized controlled trials on the effects of SGLT-2 inhibitors on UTI and genital infections demonstrated no significant difference between SGLT-2 inhibitor group and control.[20]

The reported incidence of genital infections was again highest amongst the users of dapagliflozin (76.92%) followed by empagliflozin and canagliflozin. Liu J et al, in their systemic review and meta-analysis of randomized controlled trials have clearly highlighted the risk of genital infections with the use of SGLT-2 inhibitors in comparison to controls.[20] In this study, the symptoms of DVT was minimally seen with most reported by users of dapagliflozin (23.08%) followed by canagliflozin (18.52%). The users of empagliflozin did not report any symptoms of DVT. Ueda et al, in their nationwide registry have brought similar results and demonstrated that there was no increased risk of venous thromboembolism in users of SGLT-2 inhibitors in comparison to GLP-1 agonists.[21]

The history of bone fractures was minimal (7.41%), with all the reported cases were users of canagliflozin. The results of our study commensurate with the nationwide registry by Ueda et al, who brought that there is no increased risk of bone fractures amongst SGLT-2 inhibitor users in comparison to GLP-1 agonists.[21]

The existing literature comparing the effects of individual SGLT-2 inhibitors various ADRs is conflicting and most RCTs compare individual SGLT-2 inhibitors with placebo. Hence, our study provides a basic template for comparing the various ADRs amongst the SGLT-2 inhibitors. The drawbacks of our study are it is not a randomized trial, just a cross-sectional study and was based on the memory of the users, hence subjected to bias. Hence, it is highly essential to conduct an RCT in Indian population comparing each SGLT-2 inhibitor for their ADRs and also in comparison in placebo.

CONCLUSION

SGLT-2 Inhibitors offer a unique therapeutic approach to the management of diabetes mellitus. Additional non-glycemic advantaged includes weight loss and blood pressure reduction, which may confer additional health benefits. Due to limited current post marketing data on the use of these agents, further evaluation of the safety profile and the risk-benefit analysis is the need of the hour. The present study shall provide additional information of the magnitude and clinical importance of the adverse events associated with their use. This will further elucidate the future therapeutic role of SGLT-2 inhibitors in the already rich armamentarium for the management of diabetes mellitus.

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REFERENCES

1. Unnikrishnan R, Pradeepa R, Joshi SR, Mohan V. Type 2 Diabetes: Demystifying the Global Epidemic. Diabetes. 2017;66(6):1432-42.
2. Zimmet PZ, Alberti GMM. Epidemiology of diabetes-status of a pandemic and issues around metabolic surgery. Diabetes Care. 2016;39(6):878-83.
3. Zheng Y, Ley SH, Hu FB. Global aetiology and epidemiology of type 2 diabetes mellitus and its complications. Nature Reviews Endocrinol. 2018;14:88-98.
4. Animaw W, Seyoum Y. Increasing prevalence of diabetes mellitus in a developing country and its related factors. PLoS ONE. 2017;12(11):e0187670.
5. Anjana RM, Deepa M, Pradeepa R. Prevalence of diabetes and prediabetes in 15 states of India: results from the ICMR-INDIAB population-based cross-sectional study. Lancet Diabetes Endocrinol. 2017;5(8):585-96.
6. Chawla A, Chawla R, Jaggi S. Microvasular and macrovascular complications in diabetes mellitus: Distinct or continuum? Indian J Endocrinol Metab. 2016;20(4):546-51.
7. Chaudhury A, Duvoor C, Dendi R, Sena V, Kraleti S, Chada A, et al. Clinical Review of Antidiabetic Drugs: Implications for Type 2 Diabetes Mellitus Management. Front Endocrinol (Lausanne). 2017;8:6.
8. Reusch JE, Manson JE. Management of Type 2 Diabetes in 2017: Getting to Goal. JAMA. 2017;317(10):1015-6.
9. Minamii T, Nogami M, Ogawa W. Mechanisms of metformin action: In and out of the gut. J Diabetes Investig. 2018;9(4):701-3.
10. Sola D, Rossi L, Schianca GP, Maffioli P, Bigliocca M, Mella R, et al. Sulfonylureas and their use in clinical practice. Arch Med Sci. 2015;11(4):840-8.
11. Pérez MJ, Quintanilla RA. Therapeutic Actions of the Thiazolidinediones in Alzheimer's Disease. PPAR Res. 2015;2015:957248.
12. Pakkir Maideen NM, Manavalan G, Balasubramanian K. Drug interactions of meglitinide antidiabetics involving CYP enzymes and OATP1B1 transporter. Ther Adv Endocrinol Metab. 2018;9(8):259-68.
13. Vella A. Mechanism of action of DPP-4 inhibitors-new insights. J Clin Endocrinol Metab. 2012;97(8):2626-8.
14. Nauck M. Update on developments with SGLT2 inhibitors in the management of type 2 diabetes. Drug Design, Development and Therapy. 2014;8:1335-80.

15. Lee HD. The Non-glycemic Effects of SGLT2 Inhibitor. J Korean Diabetes. 2014 Sep;15(3):151-7.
16. Basile JN. The potential of sodium glucose cotransporter 2 (SGLT2) inhibitors to reduce cardiovascular risk in patients with type 2 diabetes (T2DM). J Diabetes Complications. 2013;27(3):280-6.
17. Vasilakou D, Karagiannis T, Athanasiadou E, Mainou M, Liakos A, Bekiari E, et al. Sodium-glucose cotransporter 2 inhibitors for type 2 diabetes: a systematic review and meta-analysis. Ann Intern Med. 2013;159(4):262-74.
18. Singh M, Kumar A. Risks associated with SGLT2 Inhibitors: An Overview. Curr Drug Saf. 2018;13(2):84-91.
19. Liu XY, Zhang N, Chen R. Efficacy and safety of sodium-glucose co-transporter 2 inhibitors in type 2 diabetes: a meta-analysis of randomized controlled trials for 1 to 2years. J Diabetes Complications. 2015;29(8):1295-303.
20. Liu J, Li L, Li S, Jia P, Deng K, Chen W, et al. Effects of SGLT2 inhibitors on UTIs and genital infections in type 2 diabetes mellitus: a systematic review and meta-analysis. Sci Rep. 2017;7(1):2824.
21. Ueda P, Svanström H, Melbye M, Eliasson B, Svensson AM, Franzén S, et al. Sodium glucose co-transporter 2 inhibitors and risk of serious adverse events: nationwide register based cohort study. BMJ. 2018;363:k4365.

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