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ASSESSMENT OF CURRENT PRACTICE OF PRESCRIPTION OF SGLT2 INHIBITORS IN A TERTIARY CARE HOSPITAL- AN OBSERVATIONAL STUDY

Introduction

Sodium glucose co-transport (SGLT2) inhibitors are the newest class of oral anti-hyperglycemic agents that have been approved for the treatment of diabetes mellitus. SGLT2 inhibitors are medications that have a unique mechanism of action and lowers glucose independent of insulin. These agents are rapidly establishing their role in the treatment of diabetes. Especially in patients with type 2 diabetes not willing or not ready to be started on insulin, SGLT2 inhibitors are also another option for those patients requiring additional glucose lowering and in those with acceptable risk factor profiles.[1] Four SGLT2 inhibitors (Empagliflozin, Canagliflozin, Dapagliflozin, Ertugliflozin) have been approved by United States Food and Drug Administration (FDA) since 2013. SGLT2 inhibitors block the reabsorption of glucose in the kidney, thereby enhancing urinary glucose excretion, independent of glucose dependent insulin secretion and lowering the blood glucose level.[2]

SGLT2 inhibitors may be a useful option in obese and hypertensive patients because of their weight loss and antihypertensive benefits. Patients who are at high risk for hypoglycemia may benefit from a combination of metformin and an SGLT2 inhibitor because the risk of hypoglycemia with SGLT2 inhibitors is small when compared to insulin and sulfonylureas. SGLT2 inhibitors are contraindicated for patients with renal insufficiency (GFR < 45 mL/min/1.73m^2). However, they may be very useful without regard to diabetes duration because their action is independent of β-cell function and insulin secretion. Therefore, they can be used in patients with longstanding diabetes provided renal function is acceptable.[3]

In a meta-analysis published in 2014, 24-week reduction of HbA1c with SGLT2 inhibitors was greater in trials enrolling patients with a lower mean age, shorter duration of diabetes, and a higher baseline BMI, HbA1c, and fasting glucose. Based on recent clinical trials, reduction in HbA1c in comparison to placebo reaches its maximum at approximately 6 months and is maintained up to 1 year[1] .Treatment with SGLT2 inhibitors has been associated with a similar hypoglycemic risk as that of metformin and DPP-4 inhibitors.
Sodium-glucose cotransporter-2 (SGLT2) proteins are expressed in the proximal convoluted tubule of the kidneys. These transporters are an ideal target for the treatment of diabetes because they are

responsible for roughly 90% of filtered glucose reabsorption . The normal renal threshold for reabsorption of glucose corresponds to a serum glucose concentration of 180 mg/dL. In patients with type 2 diabetes, this threshold can increase and the expression of the SGLT2 can be up-regulated causing a maladaptive response that worsens hyperglycemia. Selective inhibition of SGLT2 inhibitors can reduce this threshold to as low as 40 to 120 mg/dL.[4][5] Comparatively, individuals with the rare "non-disease," familial renal glucosuria (FRG), have no functional SGLT2 proteins. They present with glucosuria in the presence of normoglycemia. Individuals with FRG rarely have hypotension or hypoglycemia suggesting the safety of both the short and long term use of SGLT2 inhibitors.[1][3][4]

The clinical evidence with respect to SGLT2 inhibitors in cardiac patients are complicated and still evolving based on newer clinical data. Hence , it is difficult to standardise SGLT2 inhibitors in clinical practice. The evaluation of current clinical practice in relation to use of SGLT2 inhibitors in cardiac patients helps in evolving an approach that can be used to standardise future patients.

Materials and Methods

The study is being carried out in patients who are newly being administered on either one of the SGLT2 inhibitors (Empagliflozin, Dapagliflozin, Canagliflozin). A sample of 50 prescriptions are being assessed that might provide meaningful insight into the current prescription practice to derive useful recommendations. All adult patients (over 18 years) are included in the study and those patients who were unwilling to take part in the study and those patients who are terminally ill are excluded from the study.

Once the patient was prescribed any one of the SGLT2inhibitors, the patient consent was taken followed by data collection. The data is collected in a semi-structured Performa which includes details such as:

- Patient demographics
- Medical and medication history
- Indications for SGLT2 I
- Renal history
- Cardiac history
- Agent prescribed and dosing
- Glycemic status (HbA1C)
- Co prescription of other drugs
- Follow up details

After collection of the data, the details of the prescription including the prescriber details were collected. The lab reports at the time of commencement and on follow-ups were also recorded.
The Performa is then analysed to check whether the prescription was following the American Diabetic Association guidelines. If the prescription is out of guidelines, justification from the prescriber was noted - that included, other reasons or individual interests in prescribing the drug.

The patient medical details are then recorded for another 3 follow-ups.Any discontinuation in the medication is also noted with the concerning evidence and reports.

Written informed consent was taken from patients before recruitment. Patients were made aware that their participation is voluntary and they can decide not to take part without any adverse influence on their treatment. Privacy and confidentiality of the research participants were protected.

Results

A total of 50 patients and their prescriptions were assessed, in which there were 29 male patient, 21 female patients which represents 58% and 42% respectively.

Table 1-The above table represents the percentage of males and females involved in the study.

AGE	MALE	FEMALE	TOTAL
20-29	-	-	-
30-39	2	1	3
40-49	1	5	6
50-59	8	6	14
60 OR MORE	18	9	27
TOTAL	29 (58%)	21 (42%)	50 (100%)

Majority of patients were from the cardiology department who were started newly on SGLT2i, with a total of 30 patients, 21 male patients and 9 female patients respectively. In the endocrinology department, a total of 12 patients were newly started with 5 male patients and 7 female patients, 4 male patients from Gerontology department and 4 female patients from medicine department were the 3 prescriptions were discontinued on adverse drug reactions.

It was brought to our notice that the cardiology department had the maximum users of the SGLT2 inhibitors and among the SGLT2 inhibitors, emphagliflozin was identified to be used the most .The brands preferred in case of emphagliflozin were Jardiance, glixambi(empagliflozin + linagliptin) and dapagliflozin: the brand preferred here is Oxra.

The drugs were prescribed mostly in case of patients with poor glycemic control along with the comorbidities:

- Post MI / HF / IHD
- Newly detected DM and post-MI
- CAG – PCI has done
- ACS / STEMI / CAG
- HF with LV dysfunction
- IHD / AWMI with LVEF less than 35%

The SGLT2 inhibitors were used in these cases in regards to cardiac safety. A patient who had HBA1C above 6.5 % was initiated on either of the 3 drugs here.

Figure 1- Percentage of each of the drugs used in the study

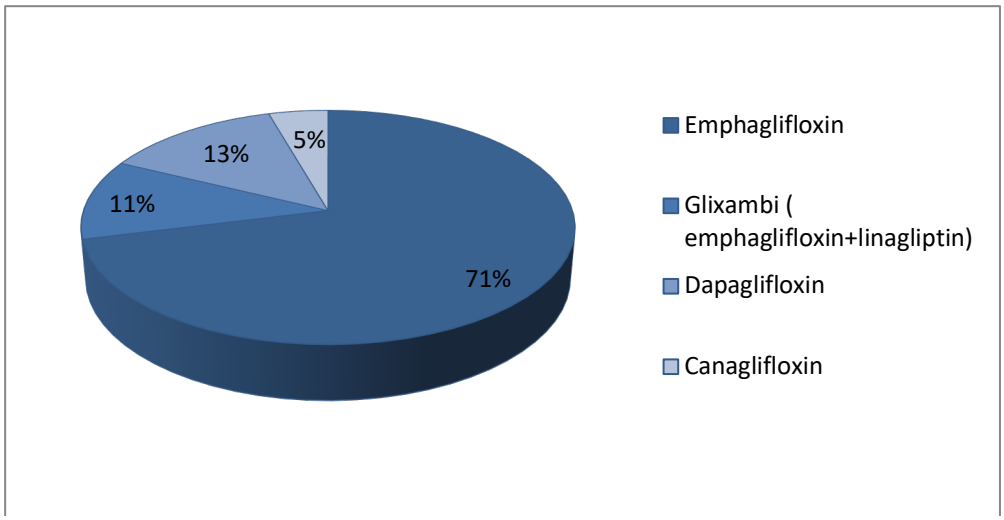


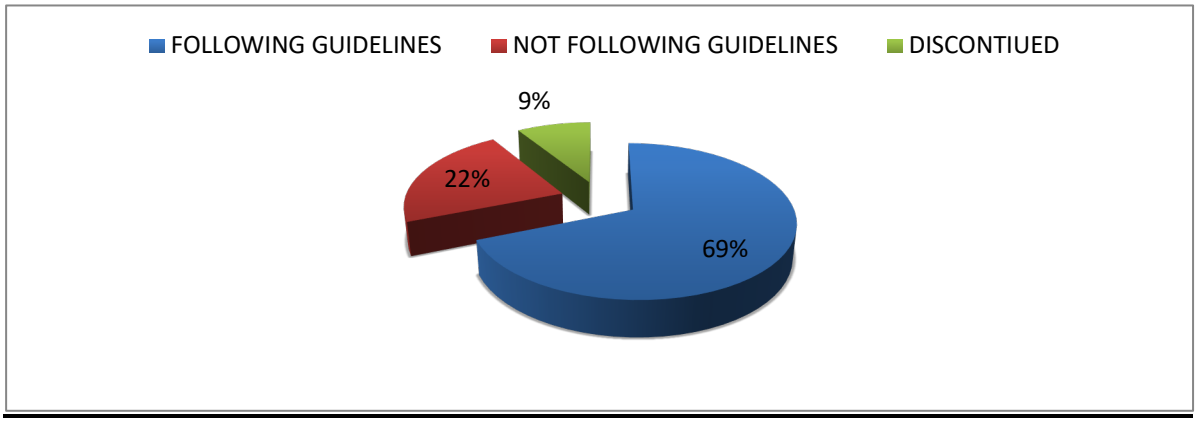
Table 2: Comorbidities to which SGLT2i are initiated (PGC-Poor glycemic control)

Sl.no	Sglt2 commenced	Probable indication	Reason for commencing
1.	Empagliflozin	Poor glycemic control (T2DM)	• AWMI S/P PTCA TO CAD • Post MI • CAD – IHD – CAG • Previous PCI • Pulmonary oedema • Ischemic cardiomyopathy • AKI • Nephrolithiasis, Nephropathy, Neuropathy • Dyslipidemia • Hypothyroidism • Overweight
2.	Glixambi (Emphagliflozin + linagliptin)	PGC	• ACS – STEMI, post wall MI, post-PTCA. • ACS – NSTEMI • Hypertrophic

			cardiomyopathy • PTCA – LAD/RCA
3.	Dapagliflozin	PGC	• Type 1 Brugada syndrome • NYHA Gr-II/III CVA with hemiparesis • Cardiac arrest survivors • Accelerated HTN • ACS • Coexisting HF, Coexisting IHD • RD • DCM • LV dysfunction • Angina
4.	Canagliflozin	PGC	• HTN • Dyslipidemia • AKI

Guidelines

Figure 2- Percentage of drugs following, not following the guidelines and discontinued during the study



Out of 50 prescription assessed 69 % of the SGLT2 drugs prescribed was following the ADA guidelines. Remaining 22% were the guidelines were not followed were justified as;

- Individual preference of the physician.
- The financial status of the patient.
- Patient choice of not taking insulin.
- To provide cardiac safety in suspected patients.
- Hypertensive patients
- Obese patients

Glycemic Status

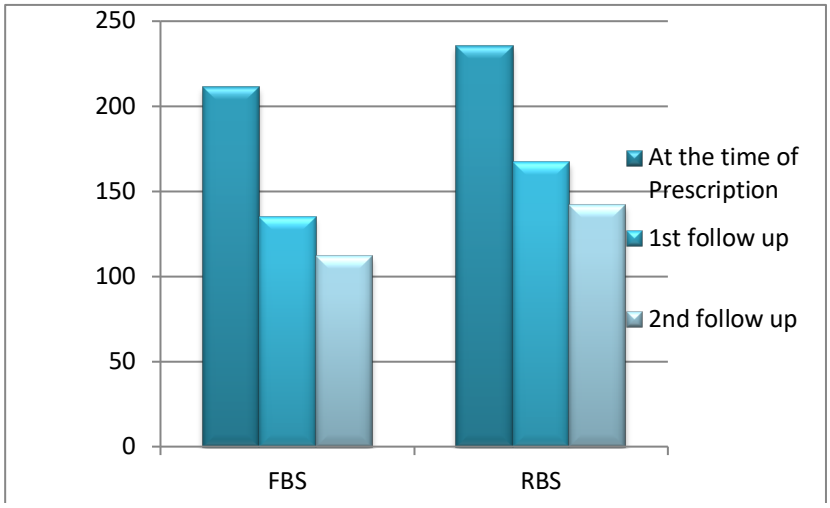
Table 3- Distribution of co-prescribed antidiabetic drug with antidiabetic class

There were 4 different classes with which the SGLT2I was given in combination with:

No.	SGLT2I	Co-prescribed Antidiabetic drugs	Co-prescribed Antidiabetic class
1.	Empagliflozin	• Galvus (Vildagliptin) • Galvus-met (Vidagliptin+Metformin) • Human mixtard • Insulin aspartate • Insulin degludec • Basal insulin analogues • Glyciphage G2(Glimepride + metformin)	• DPP4 inhibitor • DPP4I + Biguanides • Insulin • Sulphonyureas+ Biguanides
2.	Dapagliflozin	• Galvus met (Vidagliptin+Metformin) • Metformin • Inj actrapid • Glicazide • Glyciphage (Glimepride)	• DPP4I+ Biguanides • Biguanides • Insulin • Sulfonylureas
3.	Glixambi	• Glycomet (metformin) • Insugen	• Biguanides • Insulin
4.	Canaglifloxin	• Galvus (vildagliptin) • Galvus met (vildagliptin+metformin)	• DPP4 inhibitor • Biguanide + DPP4I

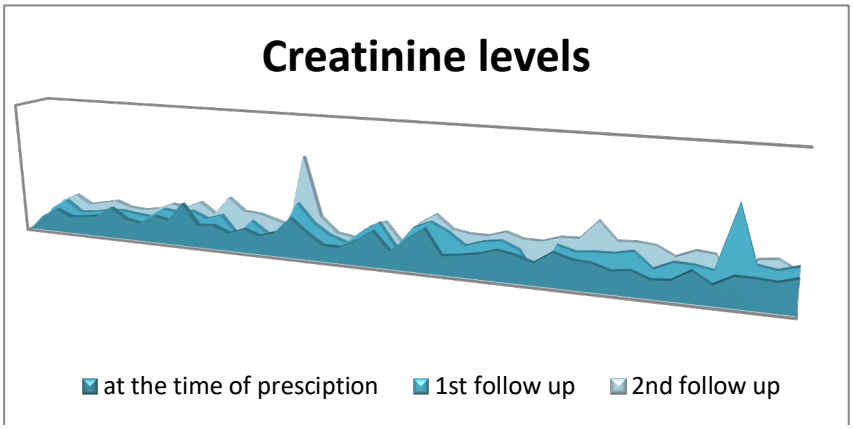
The above table represents the regiments that were followed to prescribe the sodium-glucose co-transport inhibitors. Dual therapy with SGLT2 inhibitors were initiated with biguanides class (metformin) and triple therapy mostly had the combination SGLT2I + biguanides + DPP4I.

Figure 3- Mean glycemic status



Out of 50 patients, HbA1C patients were observed and recorded. From, the above data, there is a marked decrease in the glycemic status of the patients with higher glycemic values in a duration of 3 to 6 months.

Figure 4- Representation of the creatinine spikes during each follow-up



The above table represents the Creatinine values of the study populations that were recorded as 3 values which were estimated 3 different phases, i.e creatinine at the time of commencement of the study drugs, during the 1st follow up and 2nd follow up.

It was observed in the majority of the cases there was a slight increase in the Creatinine levels of the patient and there were also cases with no particular change in the Creatinine.
Out of the 50 cases, 3 cases represented the value of creatinine very much higher than the baseline value in which one patients creatinine

was increased to 3.29 with a very short period of 2nd follow up, that which is indicated in the graph as long pointed slope.

Adverse drug reactions

- Out of the 4 different prescribed drugs, Canagliflozin was discontinued in all the patients it was prescribed as the incidence of urinary tract infection was found in patients over the use of more than 3 months.
- Empagliflozin was observed to increase the Creatinine levels in patients and was the underlying reason for discontinuation. It was also found to cause euglycemia in inpatients.
- The case was the same with Glixambi (Empagliflozin + Linagliptin), where it, also added to the fact that the incidence of the rate of the cost of the drugs is high and hence was discontinued.
- Those patients who were on dapagliflozin continued to use the medication with one reported side effect of increased creatinine and discontinuation.

Table 4- Discontinuation duration of each SGLT2I due to adverse reaction

S.No	Drugs	Duration (no. of days/months)	Reason for discontinuing
1	Empagliflozin	1 month	Euglycemia
2	Canagliflozin	4 months	UTI
3	Empagliflozin	10 days	Increased Creatinine
4	Dapagliflozin	1 month	Increased Creatinine

Table 5- Adverse reactions with causality assessment

S.No	Age /sex	Sglt2i	ADR	Causality assessment scale (WHO scale)
1.	50/Male	Empagliflozin	Increased Creatinine level	PROBABLE
2.	66/Male	Glixambi	Increased Creatinine level	PROBABLE
3.	53/Male	Dapagliflozin	Increased Creatinine level	PROBABLE
4.	54/Female	Emphagliflozin	Euglycemia (inpatient)	CERTAIN
5.	66/Female	Canagliflozin	Urinary tract	PROBABLE

			infection	

These were the adverse reactions that were observed during the study. Empagliflozin, glixambi and dapagliflozin were observed to be causing an increase in creatinine levels and were discontinued on a short period**.**

Euglycemia was observed in 2 patients who were initiated but with empagliflozin but one patient was excluded since they were on other non-allopathic medications and the other patient was discontinued empagliflozin.

Canagliflozin was prescribed only to 2 female patients among the study subjects and was found to cause UTI in both the patients and was discontinued the drug.

WHO causality assessment scale was used to the severity of the adverse drug reactions. Out of 5 ADRs identified, 4 are probable.ie, once the drug was withdrawn, it was not readministered and there is no rechallenge or dechallenge information.
The adverse reaction termed as certain, the patient, during the hospital stay has discontinued the medication due to euglycemia and later on, the discharge was readministered**.**

Discussion

SGLT2i therapy is considered alongside with other glucose-lowering medicines as an option at the first intensification of treatment for T2DM, following failure to achieve control with first-line treatment in cases of metformin intolerance.[(5)] SGLT2i medicines may also be used as add-on third-line therapies, like in combination with other glucose-lowering agents such as oral therapies or glucagon-like peptide 1 receptor agonists (GLP-1 RAs) or insulin. [(6)(7)].

In this study conducted, I assessed the use of SGLT2I in clinical practices, where the medications were assessed for their indications for a prescription which were analysed with American Diabetic Association guidelines and are reported with the details of the reasons for initiating SGLT2I outside the clinical guidelines, the various types of regimens used while prescribing SGLT2I and the various adverse drug reactions that occurred during the study time in an encounter with SGLT2I are reported and recorded.

The study showed the most used drug was empagliflozin (71%) which was majorly used in the cardiology department and endocrinology department which was followed by glixambi (empagliflozin + linagliptin) and then dapagliflozin. The least used drug observed in our clinical settings was canagliflozin.

Here according to the study, 69% of the prescriptions were following the guidelines.

What the guideline says

- ✓ According to the ADA guidelines, people with diabetes with established ASCVD, Empagliflozin decreased a composite three-point major cardiovascular event (MACE) outcome and was also shown to decrease the risk of the primary composite outcome of nonfatal myocardial infarction, non-fatal stroke, or death from cardiovascular causes in the Researching Cardiovascular Events.[(8)]The observations were finalised according to the trial conducted on empagliflozin which was named as EMPA-REG OUTCOME.

- ✓ In the EMPA-REG OUTCOME Trial, empagliflozin markedly decreased the risk of clinically important cardiovascular events (in particular, the risk of cardiovascular death), and in further hypothesis-generating analyses, it delayed the progression of CKD in people with type 2 diabetes and established cardiovascular disease. (9)

Therefore, in the study here, conducted empagliflozin and glixambi was prescribed in cases of AWMI S/P PTCA TO CAD, Post MI, CAD – IHD – CAG, Previous PCI, Pulmonary oedema, Ischemic cardiomyopathy, AKI, Nephrolithiasis, Nephropathy, Neuropathy, Dyslipidemia .

- ✓ According to guidelines, Dapagliflozin did not reach statistical significance for MACE, as in case of empagliflozin but showed a significant lowering of cardiovascular death or hospitalization for heart failure, which reflected a lower rate of hospitalization for heart failure as was observed in DECLARE-TIMI 58.(8) Dapagliflozin reduced heart failure hospitalization (HFH) and cardiovascular mortality in patients with type 2 diabetes (T2D) and HF across a wide spectrum of left ventricular ejection fraction (LVEF). The greatest benefit was found in those with HF with reduced ejection fraction (HFrEF). (10)

Here, in the study, those cases where the prescriptions were following guidelines included HF with LV dysfunction, IHD / AWMI with LVEF less than 35%, Type 1 Brugada syndrome, NYHA Gr-II/III CVA with hemiparesis, Cardiac arrest survivors, Accelerated HTN, ACS, Coexisting HF, Coexisting IHD.

- ✓ Likewise, canagliflozin reduced the occurrence of MACE in a group of subjects with, or at high risk for ASCVD. But taking on the side effects and less paper works on the drug, it was least prescribed in our study with only 2 cases.

Not following the guidelines

22% of the cases were not prescribed with regarding the guidelines. In the study conducted the reason for categorising to not following guidelines were, Individual preference of the physician. The financial status of the patient, Patients choice of not taking insulin, Inorder to provide cardiac safety in suspected patient, newly detected hypertensive cases and Obese patients.
According to the approaches to glycemic treatment, no hypoglycaemia, reducing weight, reducing blood pressure are considered as the advantages of SGLT2I and are not recommended to prescribe only for these causes. (11)

Types of regimens followed

In this study, the SGLT2I's were given in combination with four major drug classes (sulfonylurea, DPP-4 inhibitor, biguanides, and basal insulin).

If the A1C target is not achieved after approximately 3 months on monotherapy with metformin, SGLT2I can be initiated, where the choice of drug depends on a variety of patient and disease-specific factors.

In dual therapy with SGLT2I, it's confirmed to have an intermediate efficacy, low risk of hypoglycaemia, weight loss with common side effects of genitourinary infection and dehydration. The therapy with SGLT2I is considered to be very costly. (11)(12)
Triple therapy is initiated when A1C target not achieved after 3 months of dual therapy, proceeded with 3 drug combination with

metformin + SGLT2I + SU/TZD/DPP4I/Insulin.[11]

Glycemic status

The study gave a very positive outcome in the ranges of the glycemic status of the patients. The blood glucose levels were lowered into the limiting values of the normal range with mostly in the period of 3 to 4 months in the majority of the subjected patients. The HbA1C was also found to have come in the limits within a span of the 6months in most of the patients.

According to the pieces of literature, the drugs used in the study being Inhibitors of the sodium-glucose cotransporter 2, which increase renal glucose elimination, and inhibitors of 11ß-hydroxysteroid dehydrogenase 1, which reduce the glucocorticoid effects in liver and fat effectively decreases the blood glucose levels and brings the glycemic index to the favourable range. [12][13][7]

Creatinine

It was observed to have a mild to moderate increase in the values of Creatinine in the patients who are initiated on SGLT2I as observed from the study subjects. Out of 45 study subjects 3 patients had to discontinue the use of SGLT2I due to the increase in Creatinine levels.

According to the results from various works of literature acute renal failure rates were 5.4% and 5.9% in empagliflozin-treated patients [14] and the increase in Creatinine levels can be due to the pre glomerular constriction through SGLT2is and post glomerular dilation under RASis would be expected to cause an increased risk of AKI and hence elevations in the Creatinine levels. [14][15][16]

Adverse drug reactions

The study reported certain adverse reaction which includes:

Canagliflozin was discontinued in all the patients it was prescribed as the incidence of urinary tract infection.

Empagliflozin was discontinued due to the incidence of increased Creatinine levels and euglycemia and was the same as that of glixambi.

Dapagliflozin was also discontinued due to increased creatinine levels.

According to the various studies, SGLT2I's notifies ADRs as infections of the urogenital tract, ketoacidosis, and kidney damage. Cases of DKA in people treated with SGLT2is are fairly rare. Risk factors that should be considered include relatively insulin-deficient individuals (e.g. people with late-onset autoimmune diabetes who have been misdiagnosed as having type 2 diabetes), sudden reductions in insulin dose, increased requirement for insulin (due to illness, surgery or alcohol abuse), and conditions that restrict food intake, carbohydrates in particular. [17] [18]

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in eight and seven reports, respectively. Dapagliflozin was
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Genitourinary tract infections: This was the most common adverse effect seen with weakness and lethargy without

hypoglycaemia or hypotension as the second most common adverse effect after genitourinary infection. (19)(20)(21)(22)

Alteration in RFT: Patients were found to have risen in blood urea and creatinine levels within 1 month of starting drug (empagliflozin) and reported acute interstitial nephritis, where the drug was discontinued (it was secondary to gastroenteritis and fever in two patients). Serum creatinine levels gradually increased in three more patients over 12 months. Serum creatinine (mg/dL) in these patients at 6 months was 0.99, 1.1, 1.18 and at 12 months was 1.7, 1.23, 1.4, respectively. One patient had risen in serum creatinine level from 1.0 to 1.6 mg/dL at 1 month, which persisted over next month leading to discontinuation of SGLT2i. So, there was a total of nine patients with alteration in renal function. (23)(24)

Hypersensitivities to the drugs were also reported.

Conclusion

From the study, it can be concluded that 69% of the prescriptions were per the ADA established guidelines while 22% of the prescriptions were out of the guidelines either due to the advantages of SGLT2I or individual preference of the prescribers.

The study indicated a get response of the drug towards lowering the glycemic levels in the patients, at the same time the study suggests that the drug has to be monitored in a specific group of patients.

In the study, the current therapeutic practice of SGLT2 inhibitors in patients was assessed to understand and study the reason behind the prescription of sodium-glucose co-transport inhibitors and to identify the indications inside and outside the guideline, to follow the regimens followed and to learn the adverse drug reactions.

In the assessment of prescribing patterns of 50 patients, a 69% of the prescriptions were following the guidelines and 22% were prescribed out of the guidelines and less than 9% the drug was discontinued, and accordingly, the justifications given for prescribing the drug was recorded and analysed. The drugs were found to cause a decrease in glycemic level, increase in Creatinine levels and also showed urinary tract infections**.**

Limitations

All studies that are being carried out has it's own limitations and boundaries. Hence, being an observational study, this study also had its all limitations which were noted during the study period.

As this is an observational study it is difficult to define a sample size; however, a sample of 50 prescriptions provided meaningful insight into the current prescription practice but was not enough for comparing the other parameters such as the adverse reactions or events.

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