Scholars LITERATURE

La Prensa Medica Argentina

Case Report

DOI: https://doi.org/10.47275/0032-745X-122
Volume 105 Issue 3

Real World Case Study of 12 Weeks to Assess Glycemic and Non-Glycemic Changes with SGLT2I from Database of Six Type 2 Diabetic Patients

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Abstract

Background: Clinical practice guidelines are flexible when it comes to choice of therapy after using metformin in type 2 diabetes mellitus (T2DM). Sodium-glucose co-transporter inhibitors (SGLT2Is) are a new group of antidiabetic drugs which cause reduction in weight and visceral fat and waist circumference and thus lead to reduction of blood glucose level as well as decreases insulin resistance in type 2 diabetes mellitus (T2DM) patients. Whether their extra-glycemic property is retained even in real-world setting is a question that needs to be addressed.

Methods: We have follow-up data of 6 patients collected from the authors' clinic records and analyzed the effect of SGLT-2Is on anthropometric, metabolic and inflammatory parameters. Patients were treated as per the routine standard of care without any experimentation on them. The patients' physical parameters (weight, waist hip ratio), C-reactive protein, packed cell volume and Hemoglobin, HOMA-Insulin resistance and HbA1c were determined at baseline and at last follow-up visit. P-value was computed by Wilcoxon Signed Rank test.

Results: After a mean study duration of 12 weeks in six patients (meeting appropriate preset inclusion criteria), there was significant reduction in weight from 73 ± 2.48 kg (mean ± SEM) to 67.83 ± 2.32 kg (reduction of 5.17 ± 2.14; p=0.003). The significant weight reduction accompanied with significant increase in the packed cell volume (PCV) from 36.17 ± 2.05 (mean ± SEM) to 39.07 ± 1.81 (increase of 2.90 ± 2.07%; p=0.027). This supports that SGLT-2Is induces weight loss due to reduction in body fluid. The waist circumference also reduced from 106.96 ± 7.96 to 102.33 ± 5.98. The hemoglobin also increased significantly from 11.85 ± 0.6 to 12.77 ± 0.681. Other parameters such as waist hip ratio, HOMA-IR, HbA1c remained unchanged demonstrating no additional effect ofSGLT-2Is on insulin resistance.

Conclusion: In real-life scenario, this study shows that there is a statistically significant reduction in weight and waist circumference and increase in hemoglobin and hematocrit values with SGLT2I within only 12 weeks period irrespective of baseline HbA1c and any telephonic follow-up for lifestyle interventions. Real-world practice differs a lot from a randomized control Trial setting where many things are not possible to be done but these drugs maintain their extra glycemic benefits even in real world setting.

Keywords: Type 2 Diabetes Mellitus; SGLT2Is; extra-glycemic benefits; inflammatory markers; waist circumference; HOMA-IR

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Citation: Roy S, Chakraboty S (2019) Real World Case Study of 12 Weeks to Assess Glycemic and Non-Glycemic Changes with SGLT2I from Database of Six Type 2 Diabetic Patients. Prensa Med Argent, Volume 105:3. 122. DOI: https://doi.org/10.47275/0032-745X-122.

Received: February 04, 2019; **Accepted:** February 26, 2019; **Published:** February 28, 2019

Introduction

Type 2 diabetes mellitus (T2DM) has recently become a global health issue by ranking 9th in the list of major death causes. Since the last three decades, individuals tested with T2DM have been on increasing trend.T2DM global epidemic is believed to rise from 2.8% (in 2000) to 4.4% (in 2030), taking into consideration all age groups.

Asia has been a hotspot for high incidence of T2DM as a worldwide epidemic, with countries like China and India taking the lead. There is large variation in state-specific diabetes prevalence in India. Dietary habits like consuming more red meat, refined grains and beverages with added sugar are considered to have a significant effect in T2DM epidemic causing overweight condition [**1**].

Health complications related to cardiovascular and renal systems leads to high rates of morbidity and mortality. Many therapeutic options are available to treat T2DM since few decades. However, the disadvantages of using insulin-dependent treatment options are still prevalent. The mechanism of action exhibits many side effects like hypoglycemia, weight gain and low renal functionality. Furthermore, weight gain as well as hypertension leads to the condition of obesity and cardiovascular morbidity. Many researchers are now focusing on new drug classes that would effectively lower the glucose level in blood independently of insulin, as they might result in improved acceptability and sustainability. In light of this, the sodium glucose cotransporter 2 (SGLT2I) has been developed as a treatment option for T2DM patients with chronic renal dysfunctionality and cardiovascular diseases [**2**].

SGLT2I plays a crucial role in lowering HbA1c levels, blood pressure and weight loss.This in turn lowers the risk of hospitalization due to heart ailments and renal complications in T2DM patients. With declining kidney function, SGLT2Is' impacton blood glucose control is attenuated **[3]**.

Case study

Inclusion criteria: Type 2 diabetics, HbA1c more than 6.5%

Estimated Glomerular Filtration Rate (as per CKD-EPI) >/=45 ml/min/1.73m2

Duration of diabetes is more than 2 years at least

Patients had no changes in their treatment during this study period

Stable therapies for all diseases for at least 6 months prior to study Onset

No prior history of any SGLT2I uses in last 6 months

Exclusion Criteria: Any history of Myocardial Infarction or Acute Coronary Syndrome, acute kidney injuryin last 3 months of study onset.

No history of smoking at baseline or during study

No travelling to high altitudes during the study

No history of any drug intake that might affect the body or blood Parameters

No concurrent illness or inflammation at baseline that might affect blood markers

The study population included four males and two females who had the history of T2DM for more than two years and HbA1C>6.5% initiated on either Empagliflozin 25 or Dapagliflozin 10. Baseline demographic and metabolic variables were collected at the time of SGLT2I initiation. The concomitant medications taken by the patients along with the study drug are summarized in **(Table 1)**. Baseline characteristics of the patients and changes in their physical and hemodynamic parameters over 12 weeks of follow-up after SGLT2I initiation are summarized in **(Table 2)** (P value computed by Wilcoxon Signed Rank test). We observed that there has been a significant weight reduction accompanied with statistically significant decrease in Waist circumference (p=0.048) and significant increase in the PCV from 36.17 ± 2.05 (mean ± SEM) to 39.07 ± 1.81 (increase of 2.90 ± 2.07%; p=0.028) as well as significant rise in Hemoglobin percentage (p=0.027). **(Table 3)** summarizes the mean change in the hemodynamic and metabolic parameters over the follow-up period taking into consideration the statistical values.

Discussion

T2DM is associated with multiple chronic complications. Since decades, research has been focused on developing novel treatment modules for T2DM. One of the major discoveries in this field is SGLT2I, which possess remarkable glycemic as well as non-glycemic clinical advantages in treating T2DM patients.

SGLT2 led to release of glucose in urine that led to weight loss and decrease in body fat. Adiposity possesses a great risk in development of cardiovascular disease. Hence, reduction in weight not only reduced this risk but also plays a crucial role in reduction of blood pressure and lipid when observed with SGLT2 inhibitor therapy. In addition to this,modest reduction in weight is observed in T2DM patients treated with empagliflozin drug groups during EMPA-REG OUTCOME (w2 kg), which further contributed to reduction in cardiovascular mortality rate **[4,5]**.

Variation in weight of the subjects of current study (1.5 kg) was found to be highly significant when its baseline value (85.7 ± 17 kg) was compared with the follow-up period (6 months) value (84.2 ± 16.6 kg, P=0.0001). Similar findings were observed while comparing baseline weight in the Emirati population (85.7 ± 17.8 kg vs. 84 ± 17.2 kg, P=0.0001), which was found to be consistent in the previous study in which SGLT2I's efficacy was studied in reduction of glycated hemoglobin and weight loss in these Emirati T2DM patients **[6]**.

Clar and colleagues carried out systematic meta-analysis of clinical trials with dapagliflozin and canagliflozin. The study outcome stated reduction in the levels of HbA1c by 0.54% when treated with dapagliflozin when compared with placebo. However, when treated with canagliflozin, comparatively more decrease in levels of HbA1c was observed when compared to sitagliptin (by 0.21%). Administration of both the drugs showed decrease in body weight in a consistent manner (Dapagliflozin=1.18 kg; canagliflozin=2.3 kg) **[7]**.

Normally all SGLT2I show a decrease in CRP levels due to their decrease in insulin resistance (IR) level. In our study, there was a slight

Table 1: Treatment received by the 6 Type 2 diabetic patients.

Name	Initial treatment	Changes
SL 1	Empagliflozin 25; aspirin 75; rosuvastatin 10; LT4 75microgm	None
SL 2	Empagliflozin 25; Dulaglutide 1.5/week; aspirin 75; atorvastatin 10; Metoprolol 50 XR	None
SL 3	Empagliflozin25; glimepiride 0.5; teneligliptin20	None
SL 4	Empagliflozin 25; metformin XR 1; pioglitazone 15; teneligliptin 20; Aspirin 75; atorvastatin 20; telmisartan 80	None
SL 5	Empagliflozin 25; metformin XR 1; pioglitazone 15; teneligliptin 20; Aspirin 75; atorvastatin 20; telmisartan 80	Increased the dose of insulin
SL 6	Dapagliflozin 10; metformin XR 1; glimepiride 1; teneligliptin 20	None

Table 2: Baseline characteristics evaluation during SGLT2I initiation and determination of change in mean hemodynamic and metabolic parameters over follow-up.

NAME	WEIGHT	WAIST:HIP	HOMA-IR	CRP	PCV	Hb	HbA1c
SL 1	80	102:100	2.78	1.0	35.3	11.3	7.1
SL 2	72	120:118	0.68	1.5	33.1	10.6	7
SL 3	72	101:96	1.31	2.8	36	12	7.6
SL 4	68	98:101	1.14	5.9	35.7	11.8	7.9
SL 5	66	107:112	2.35	2.8	31.2	10.4	8.5
SL 6	80	110:102	1.27	19.5	45.7	15	6.6

Baseline Parameters

Table 3: Mean changes in hemodynamic and metabolic parameters over follow-up.

		Mean	Std. Error Mean	p
Pair 1	WEIGHT-Baseline	73.00	2.408	0.003
	WEIGHT-Follow-up	67.83	2.315	
Pair 2	WAIST CIRCUMFERENCE--Baseline	106.96	7.96	0.048
	WAIST CIRCUMFERENCE-Follow-up	102.33	5.98	
Pair 3	WAIST:HIP--Baseline	1.015	.019	0.925
	WAIST:HIP--Follow-up	1.016	.014	
Pair 4	HOMA-IR--Baseline	1.59	0.33	0.320
	HOMA-IR-Follow-up	1.37	0.27	
Pair 5	CRP--Baseline	5.58	2.86	0.237
	CRP-Follow-up	2.63	0.76	
Pair 6	PCV--Baseline	36.17	2.05	0.028
	PCV-Follow-up	39.07	1.81	
Pair 7	Hb-Baseline	11.85	.681	0.027
	HB-Follow-UP	12.77 .600	.600	
Pair 8	HbA1c-Baseline	7.45	.281	0.173
	HbA1c-Follow-up	0.173	.570	

reduction in CRP; however it was not statistically significant. There was no follow-up and the reason for no reduction in CRP might be due to lifestyle changes as well as any concomitant infection for which they did not seek medical advice or report at the clinic.

Due to the increase in the diuretic effect of SGLTL2 inhibitors, its use in clinical practice is greatly increased. On initiation of the SGLT2I therapy, there is immediate increase in urine output and sodium excretion. Also, there is increase in hematocrit after SGLT2I administration. A recent study has been published which indicates that the diuretic effect of SGLT2I are not the only factor of rise in the hematocrit values in a diabetic patient. Based on the results of randomized study Dapagliflozin may lead to increase in production of red blood cell production by suppressing plasma levels of hepcidin (a pro-inflammatory inhibitor of iron transport). This might be a new mechanism which possibly leads to increase in hematocrit levels with SGLT2 Inhibitor treatment.

The initial part of increase is due to the diuretic effect but the later part is attributed by the rise in erythropoietin levels.

With administration of SGLT2-dapagliflozin drug in T2DM patients, increased levels of hemoglobin and hematocrit are observed due to increased erythropoiesis. Increased Hematocrit level in EMPAREG outcome (Trial number NCT01131676) has been attributed to be a major CV benefit contributing factor **[8]**. Recently Sano et al. has proposed that the increase in EPO levels with SGLT2Is could be due to recruitment of neural-crest derived fibroblasts producing EPO which stops getting converted to myofibroblasts due to reduction in proximal tubular oxygen consumption **[9]**. Another proposed mechanism is hypoxia at the level of corticomedullary junction due to afferent arteriolar constriction by SGLT2Is.

The baseline HbA1c level was 7.45 ± 0.2, which dropped to 6.82 ±0.5 at 12 weeks (P=0.1). This particular effect was found to be independent of the age of the patients, their gender and duration of diabetes, other comorbid conditions and use of other drugs. This drop in HbA1c in 3 months has been seen in many studies and exhibits a novel mechanism of SGLT2Is, which do not need functioning beta islets cells **[10]**.

Monotherapy treatment approach of T2DM using dapagliflozin drug only is used with inadequately controlled lifestyle. The subjectsexhibited a low level of HbA1c which was highly significant when compared to placebo group when treated with dapagliflozin (5 mg and 10 mg; P<0.001 and <0.0001, respectively) **[11]**.

A recent review on clinical trials using dapagliflozin, canagliflozin, luseogliflozin, ipragliflozin and tofogliflozin was conducted [7]. The results of all the trials showed thatadministration of SGLT2Is in mono, dual or triple therapy seems to behighly efficient in gaining HbA1c value <7% **[2,3]**. As per a pooled data analyses from 2286 T2DM patients, five randomizedand placebo controlled, phase III clinical trials were considered for analysis of empagliflozin's effect on HbA1c, blood pressure andweight. Also, the HbA1c reduction decreased with the decrease in the baseline estimatedglomerular filtration rate (eGFR) **[3]**.

This study exhibited significant effects of SGLT2 on various clinical parameters. In addition to this, it was well tolerated across eGFR subgroups.

Conclusion

In real-life scenario, administration of SGLT2I resulted in statistically significant decrease in the weight and waist circumference and significant increase in hemoglobin and hematocrit within 12 weeks period irrespective of baseline HbA1c and any telephonic follow-up for lifestyle interventions.

Real-world practice differs a lot from a Randomized Control Trial setting where many things are not possible to be done but these drugs maintain their extra-glycemic benefits irrespective of any Randomized Trial setting.

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