Journal of Cardiovascular Disorders

Open Access

Austin Publishing Group

Research Article

A Longitudinal Study on Hematocrit Changes after Glifozins Exposure in Patients with Type 2 Diabetes

De las Nieves López MA*, Robles Mateos C, Soria Cano JJ, Barón Fernandez O, Dominguez Lomeña MJ and Palomo Hernandez AM

Instituto de Gestión Sanitaria (INGESA), Área Sanitaria de Melilla, Melilla, España, Spain

***Corresponding author:** Miguel Angel de las Nieves, Instituto de Gestión Sanitaria (INGESA), Área Sanitaria de Melilla, CN Policía s/n-52006 Melilla, Spain

Received: May 29, 2021; **Accepted:** July 05, 2021; **Published:** July 12, 2021

Abstract

Background and Methods: Gliflozins are widely prescribed drugs in patients with type 2 diabetes. We pursue to explain abnormal increments in red cell parameters observed in this population, by means of a longitudinal study in 149 patients with a gliflozins exposure period of 12±6 months. Red cell parameters, HbA1c and other variables were recorded.

Results: HbA1c fraction decreased (-0.5±1.3, 95% CI: -0.7 to -0.3, p<0.001), while mean hemoglobin (0.5±0.9, 95% CI: 0.3 to 0.6, P<0.001) and hematocrit (1.6±2.6, 95% CI: 1.2 to 2.0, P<0.001) increased. Mean (SD) hematocrit increased 2.7±1.9 in 112 patients, and decreased -1.7±1.5 in 37 (p<0.001 for subgroup differences). The larger increments in PCV were proportional to higher plasma fraction at baseline (p=0.009).

Conclusion: Red cell parameters after gliflozins exposure tend to increase and may reach abnormally high thresholds in some patients with type 2 diabetes.

Keywords: Type 2 diabetes; Gliflozins; Red cells; Hematocrit

Introduction

Hemoglobin (Hb) >16.5 g/dL and >16 g/dL or hematocrit >0.49 and >0.48, in males and females respectively, serve as major criteria to diagnose Polycythemia Vera [1]. These thresholds are sensitive to detect this condition, but more strict criteria in males (hematocrit >0.52) are used by some scientific organizations [2], and are more specific as predictors of adverse outcomes [3].

Here we report a preliminary observation of some patients referred for investigation because abnormally high hematocrit, or Packed Cell Volume (PCV), which after assessment were considered secondary and probably linked to gliflozins (Table 1). Thereafter, an explanatory analysis was performed by means of a retrospective longitudinal study, to assess if these changes are possible in type 2 diabetes patients receiving these drugs. Gliflozins are widely used oral antidiabetic agents inducing urinary glucose loss by means of Sodium Glucose Cotransporter 2 inhibition (SGLT2i), which show benefit for Cardiovascular (CV) outcomes in patients with type 2 diabetes [4]. The increment in red cell parameters was the main mediator of these drugs reducing mortality and hospitalization for heart failure in this population [5,6].

Material and Methods

Preliminary observation

During year 2019, several patients with a high PCV were assessed for clonal erythrocytosis with *JAK2 V617F* gene mutation analysis and erythropoietin serum levels with negative results. Risk factors for increased PCV were recorded and served as template for further analysis (Table 1), and a link to gliflozins was suggested.

Setting

Public Health System (INGESA) in Spain covering an insured population of 74420 citizens. Active prescription of gliflozins during the first semester of year 2020 was retrieved in 804 patients from our pharmacy database (canagliflozin 202, dapagliglozin 306 and empagliflozin 296).

Inclusion criteria

Patients with type 2 diabetes and a new prescription of gliflozins during years 2018 and 2019, with drug exposure for 12±6 months. Patients with baseline anemia (PCV<0.34) were excluded, and patients in our preliminary observation were deliberately not included.

Sample size and data set

In order to detect differences of ±4 between mean baseline and after treatment PCV with a 95% confidence interval, 163 records were initially selected. Continuous variables recorded include age, baseline and after exposure Hb, PCV and HbA1c fraction, as well as their differences. Gender, smoking status, diuretic use, history of hypertension, body mass index score and gliflozin type were recorded as categorical.

Laboratory methods

A central laboratory is used for the entire population covered. Briefly, blood samples anticoagulated with EDTA were analyzed on a Mindray® BC-6800 hematology analyzer, and the same sample was used for HbA1c measurement with the G8 HPLC device (Tosoh Bioscience®). Clinical record management and laboratory data are linked by Modulab_Gold® as laboratory information system.

Statistical analysis

Student´s t test was used for paired samples to compare changes from baseline and after exposure Hb, PCV and HbA1c, and analysis of its variance (ANOVA) to compare mean changes according to gender, tobacco use, hypertension, weight score, diuretics use or gliflozin molecule. Risk factors for PCV >0.48, or increasing it ≥3 points after exposure were explored by its association to continuous

Citation: De las Nieves López MA, Robles Mateos C, Soria Cano JJ and Barón Fernandez O. A Longitudinal Study on Hematocrit Changes after Glifozins Exposure in Patients with Type 2 Diabetes. J Cardiovasc Disord. 2021; 7(1): 1044.

Table 1: Clinical characteristics in six selected males with type 2 diabetes receiving gliflozins referred for investigation.

	Canagliflozin		Dapagliflozin		Empagliflozin	
Patient	1	2	3	4	5	6
Age at presentation (years old)	61	60	60	61	74	56
Hypertension	Grade I	Normal high	Grade II	Normal high	Grade II	Grade I
Obesity	Class I	Class II	Not stated	Class II	Class I	Class I
Current smoker	Yes	Yes	Yes	Yes	No	Yes
Baseline Hct†	0.47	0.47	0.49	0.5	0.49	0.45
Peak-observed Hct‡	0.55	0.52	0.57	0.54	0.58	0.5

†Mean value observed for previous determinations before treatment with any gliflozin was started.
‡The highest value ever observed after treatment with gliflozins for at least 12 months (patients 1 to 5), or six months (patient 6).

or categorical variables, by means of chi-square test and logistic regression. The analysis was performed with SPSS package (IBM, V22).

Results

After applying exclusion criteria to our initial 163 patients, 149 were available for the final data set analysis, balanced for gender (49% females *vs.* 51 % males). Their mean age was 62.56±10,6 years old; 57% of patients had a history of hypertension, 25.5% used diuretics and 17% were current smokers. Only 20% of patients were normal for body mass index, and canagliflozin (n=20, 13.4%) was underrepresented compared to dapagliflozin (n=66, 44.3%) and empagliflozin (n=63, 42.3%).

Outcome measures

After gliflozin exposure, HbA1c fraction decreased (-0.5±1.3, 95% CI: -0.7 to -0.3, p<0.001), while mean hemoglobin (0.5±0.9, 95% CI: 0.3 to 0.6, P<0.001) and PCV (1.6±2.6, 95% CI: 1.2 to 2.0, P<0.001) increased. Female gender was more likely to present larger increments in red cell parameters, particularly hemoglobin (+0.7 gr/dL *vs.* +0.3 gr/dL, p=0.04), as shown in Table 2. When PCV was analyzed by subgroups defined as a reduction or increment of PCV after exposure, the mean change for those that did not reduce PCV was +2.7, and -1.7 for those showing a reduction (Table 3).

Risk factors for PCV ≥0.48 after exposure

Before gliflozin prescription, 12 patients (8%) presented PCV ≥0.48 and only one PCV >0.5 (0.507), rising to 19 (12.7%) after exposure; of these, 11 presented PCV>0.5 and 4 >0.52. Male gender (OR 16, 95% CI 2.2-119), and baseline PCV (p=0.002) were the only factors significantly associated to this outcome.

Risk factors for increments >3 points in PCV

A total of 40 patients presented this outcome, and only 2 of them were smokers (p=0.01). On multivariate regression analysis, gender (p=0.44), hypertension (p=0.7), gliflozin molecule or weight (p>0.15 for all scores) were independent of this outcome, but it was dependent on initial PCV (p= 0.009) and smoking status (p=0.05). The lower baseline PCV the higher its increment, and being a smoker showed a lower risk to increase PCV >3 points (OR 0.19, 95% CI 0.04- 0.83).

Subgroup analysis

A decrease in PCV after gliflozin exposure was observed in 37 patients, but their final mean HbA1c was similar to those showing an increase (7.2 *vs.* 7,4, p=0.35). Female gender showed lower risk to decrease PCV (OR 0.4, 95% CI: 0.18-0.88, p=0.02), as did non-smokers (OR 0.37, 95% CI: 0.15-0.89, p=0.03) and those without hypertension (OR 0.4, 95%CI: 0.18- 0.90; P=0.03).

When only patients increasing PCV were considered, this increment was ≥3 in 40 of 112 patients (35.7%) without differences for gender, hypertension, diuretic use, weight or SGLT2 molecule. Non-smokers showed a trend to increment PCV >3 (p=0.07). Whithin the subgroup showing an increment, it was ≥3 but <5 in 28 /112 patients (25%), and ≥5 in 12/ 112 (10.7%), or 28/149 (18.8%) and 12/149 (8%) of the entire cohort respectively.

Discussion

Our results show that at least 27% of real world type 2 diabetes patients receiving gliflozins may exhibit increments in PCV >3 points and, depending on initial PCV, some may reach abnormally high values. Volume status and anemia are therapeutic targets for type 2 diabetes patients with heart or kidney conditions, and plasma volume contraction by osmotic diuresis and increased endogenous erythropoietin may partly explain the beneficial CV effects of these drugs and changes in red cell parameters [7,8].

The mean (SD) PCV increment in our study (1.6±2.6) is consistent with those published for gliflozins, despite different inclusion criteria, variable length of treatment, gliflozin molecule and strength. Empagiflozin showed a dose and time dependent increase in adjusted mean (±SE) PCV of 2.18 (0.08) to 2.66 (0.14) in a mediation analysis assessing its beneficial effect on mortality in patients with type 2 diabetes and high CV risk [5], and a similar mean

Table 2: Measured outcomes after exposure to gliflozins according to gender.

	Baseline Mean (SD)			After exposure Mean (SD)			Differences Mean (SD)		
	Female	Male	p	Female	Male	p	Female	Male	p
Hb (g/dL)	13.2 (1.1)	14.8 (1.3)	<0.001	13.8 (1)	15.1 (1.4)	<0.001	0.7 (0.9)	0.3 (0.9)	0.04
PCV (%)	40.2 (2.9)	44.3 (3.3)	<0.001	42.2 (2.7)	45.5 (4.1)	<0.001	2 (2.2)	1.3 (2.9)	0.1
Hb A1c (%)	7.8 (1.5)	7.8 (1.7)	0.9	7.4 (1.1)	7.3 (1.1)	0.3	-0.3 (1.6)	-0.6 (1.4)	0.3

Table 3: Overall changes in PCV (%) and subgroup analysis for those showing an increment or reduction after exposure to gliflozins.

Overall (n=149) Mean (SD)		Subgroup analysis		P for differences among subgroups (ANOVA)
		Increment (n=112) Mean (SD)	Reduction (n=37) Mean (SD)	
Baseline	42.3 (3.7)	41.6 (3.7)	44.4 (2.8)	<0.001
Last record	43.9 (3.8)	44.3 (3.9)	42.7 (3.2)	0.027
Difference	1.6 (2.6)	2.7 (1.9)	-1.7 (1.5)	<0.001

(±SE) increment of 2.53 (±0.05) was reported for canagliflozin in a mediation study to explain its beneficial effect on heart failure [6]. The least square mean increment (±SD) was 2.31±3.9 for dapagliflozin in diabetes and non-diabetic patients with heart failure, where male population was 77%, mean Hb 13.6 g/dL, and 33.6% in the diabetes male cohort presented anemia [9]. Thus, the expected effect of giflozin therapy is an increment in PCV, and not becoming anemic as a direct consequence of these drugs. In our study, the mean (SD) increment was 2.7±1.9, when only patients showing a raised PCV after exposure were considered.

Our sample was balanced for gender, and the mean (SD) baseline hemoglobin was 14.0±1.4 and PCV 42.3± 3%, higher than in gliflozin trials reporting red cell parameters. In patients with very high CV burden, empagliflozin induced a mean (±SD) increment in PCV of 4.8±5.5 to 5±5.3 [10]. When compared to our study, 71% of patients in this trial were males, mean baseline Hb and PCV were lower (13.4±1.5 and 41.1±5.7 respectively), mean baseline HbA1c was slightly higher (8.07±0.8 % *vs.* 7.8± 1.6 %), on therapy follow-up was longer (30 months *vs.* 12±6 months), and diuretic use was higher (43.7% *vs.* 25.5%).

Our finding that the lower the baseline PCV (higher plasma volume) the higher its increment after exposure to gliflozins, could be a clue to their net clinical benefits. Anemia is considered a risk factor for CV outcomes and gliflozins must be considered anti-anemic drugs, but red cell parameters above normal may also increase this risk, particularly females with Hb >14 g/d [11], or males with Hb >16 g/dL [12]. The benefit of theses drugs preventing or improving heart failure in patients with CV morbidity is well established, but the reduction of ischemic atherosclerotic events is less robust [13]. Avoiding dehydration is highly recommended in this patient population and its association to stroke has been suggested [14], and PCV may serve as a direct measurement of hydration and blood viscosity. However, the global incidence of stroke in gliflozin trials in diabetes type 2 patients does not seem to be increased [15].

We excluded anemic patients in our analysis because we were not measuring the effect of these drugs on anemia and its important clinical benefit. However, despite this exclusion a subset of our patients may show abnormal increments in red cell parameters, and it does translate to abnormally high PCV in some patients. In fact, 7.4% of our cohort presented PCV >0.5 after exposure *vs.* 0.7% before prescription, and a high baseline value was the main determinant of this outcome. Despite an overall neutral effect of gliflozins on stroke rates, increasing PCV beyond normal limits may not be desirable in type 2 diabetes patients with CV risk factors. Of note, a similar increment would clearly benefit anemic patients in clinical trials, and it could offset the potential increased risk of PCV elevation on ischemic events.

An important subset of subjects in our study (37/149, 24.8%) showed a decrease in PCV after drug exposure. Male gender, hypertension and smoking were the highest risk factors for this outcome and must represent higher morbidity and ongoing illness, such as infection, surgery, or abnormal bleeding as common causes of anemia in the community. Again, this subgroup analysis was not performed in clinical trials, and it clearly counterbalance the overall increments reported in PCV, which actually is the expected effect of gliflozins.

Our study has limitations. First, no clinical outcomes have been measured, however we were trying to explain laboratory abnormalities and therefore our outcome measures are mainly analytical. Second, antithrombotic medication was not recorded, and this variable may be relevant to explain some observed cases showing a reduction in PCV presenting as severe acquired iron deficiency anemia. Third, we did not measure renal function changes because the possibility that it could modify our outcomes in the established period of observation was low. Nevertheless, our results are valid to explain abnormally high PCV in diabetes type 2 patients treated with gliflozins, as suggested in our preliminary observation.

Conclusion

In conclusion, we have shown that gliflozins may cause important increments of PCV in real world clinical practice, and that higher increments are to be expected for those with the larger plasma volume. For patients with high baseline PCV, these drugs may not confer maximal CV benefit, as potential plasma volume contraction and erythropoietin response is probably limited, and when it occurs it will be at the expense of increasing it to pathological thresholds. This is important to know for internal medicine, hematology, diabetes and heart failure physicians, in order to adapt the application of evidence from clinical trials to individual subjects, so avoiding patient safety concerns, unnecessary studies and potential harm. The definition of safety limits in PCV for patients receiving gliflozins would be highly recommended, but until further research is available, some caution should be considered in type 2 diabetes patients with baseline PCV ≥0.48 exposed to these drugs.

Acknowledgement

This study has been possible with the support of "Unidad Docente" and "Farmacia de Atención Primaria " in Área Sanitaria de Melilla.

References

1. Arber DE, Orazi A, Hasserjian R, Thiele J, Borowitz MJ, Le Beau MM, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasm and acute leukemia. Blood. 2016; 127: 2391-2405.

2. McMullin MF, Harrison CN, Ali S, Cargo C, Chen F, Ewing J,et al. A guideline for the diagnosis and management of polycythaemia vera. A British Society

for Haematology Guideline. Br J Haematol. 2019; 184: 176-191.

3. Wouters H, Mulder R, van Zeventer IA, Schuringa JJ, van del Klauw, van der Harst P, et al. Erythrocytosis in the general population: clinical characteristics and association with clonal hematopoiesis. Blood advances. 2020, 4: 6353-6383.

4. Das SR, Everett BM, Birtcher KK, Brown JM, Januzzi JL, Kalyani RR, et al. Expert consensus decision pathway on novel therapies for cardiovascular risk reduction in patients with type 2 diabetes: a report of the American college of cardiology solution set oversight committee. J Am Coll Cardiol. 2020; 76: 1117-1145.

5. Inzucchi SE, Zinman B, Fitchett D, Wanner C, Ferrannini E, Schumacher W, et al. How does empagliflozin reduce cardiovascular mortality? Insights from a mediation analysis of the EMPA-REG OUTCOME trial. Diabetes Care. 2018; 41: 356-363.

6. Li JW, Woodward M, Perkovic V, Figtree GA, Heerspink HJL, Mahaffey KW, et al. Mediators of the effect of canagliflozin on heart failure in patients with type 2 diabetes. J Am Coll Cardiol HF. 2020; 8: 57-66.

7. Mazer CD, Hare GMT, Connelly PW, Gilbert RE, Shehata N, Quan A, et al. Effect of empagliflozin on erythropoietin levels, iron stores, and red blood cell morphology in patients with type 2 diabetes mellitus and coronary artery disease. Circulation. 2020; 141: 704-707.

8. Lopaschuk GD, Verma S. Mechanism of cardiovascular benefits of sodium glucose co-transporter 2 (SGLT2) inhibitors. JACC Basic Transl Sci. 2020; 6: 632-644.

9. McMurray JJV, Solomon SD, Inzuchi SE, Kober L, Kosiborod MN, Martinez FA, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. New Eng J Med. 2019; 381: 1995-2008.

10. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Eng J Med. 2015; 373: 2117-2128.

11. Panwar B, JuddS, Warnock DG, McCleland WM, Booth JN, Muntner P, et al. Hemoglobin concentration and risk of incident stroke in community-living adults. Stroke. 2016; 47: 2017-2024.

12. Lee G, Choi S, Kim K, yYun JM, Son JS, JeonSM, et al. Association of hemoglobin concentration and its change with cardiovascular and all cause mortality. J Am Heart Assoc. 2018; 7: e007723.

13. Sinha B, Ghosal S. Sodium-glucose cotransporter-2 inhibitors (SGLT-2i) reduce hospitalization for heart failure only and have no effect on atherosclerotic cardiovascular events: a metaanalysis. Diabetes Ther. 2019; 10: 891-899.

14. The Committee on the proper use of SGLT2 inhibitors. Recommendations on the proper use of SGLT2 inhibitors. J Diabetes Investig. 2020; 11: 257-261.

15. Guo M, Ding J, Li J, Wang J, Zhang T, Liu C, et al. SGLT2 inhibitors and risk of stroke in patients with type 2 diabetes. Diabetes Obes Metab. 2018; 20: 1977-1982.