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International Journal of Geriatrics and Gerontology

Research Article

Higashikawa T, et al. Int J Geriatr Gerontol 5: 124.
DOI: 10.29011/2577-0748.100024

The 12-Month Administration of Tofogliflozin for Glycemic Control with Monitoring Electrolytes, Renal and Cardiac Function in Japanese Elderly Patients with Type 2 Diabetes Mellitus

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Citation: Higashikawa T, Ito T, Mizuno T, Ishigami K, Kohori M, et al. (2021) The 12-Month Administration of Tofogliflozin for Glycemic Control with Monitoring Electrolytes, Renal and Cardiac Function in Japanese Elderly Patients with Type 2 Diabetes Mellitus. Int J Geriatr Gerontol 5: 124. DOI: 10.29011/2577-0748.100024

Received Date: 16 January, 2021; **Accepted Date:** 27 January, 2021; **Published Date:** 03 February, 2021

Abstract

Objective: Tofogliflozin, a new class of glucose-lowering drugs, acts on sodium glucose cotransporter 2 locating on proximal tubules of kidney, excreting excessive glucose by inhibiting the transporter. Due to its mechanism of osmotic diuresis, monitoring of electrolyte and dehydration is important. The present study investigated a time-dependent change of these variables in elderly people.

Methods: The treatment was conducted in 81 elderly patients with type 2 diabetes mellitus receiving tofogliflozin for 12 months. Glycated hemoglobin (HbA1c), serum electrolytes (sodium, potassium, chloride) and hematocrit as an index of dehydration were continuously monitored during the investigation period.

Results: HbA1c significantly decreased ($\beta1=7.26$, $\beta0=-0.04$, $p<0.01$, by linear regression analysis). Electrolytes, including sodium, and chloride, significantly changed throughout the investigation period.And heamtocrit potassium,eGFR,and BNP did not change throughout the period.

Conclusion: A twelve-month administration of tofogliflozin improved glycemic control in type 2 diabetic patients without aggravating the abnormality of serum electrolyte concentration and hematocrit values. This study suggested that 12-month administration of tofogliflozin exhibited glucose-lowering with less risk of drug-induced electrolyte abnormalities, dehydration and aggravating BNP level in elderly patients with type2 diabetes mellitus.

Keywords: BNP; Elderly Patients; Electrolyte; HbA1c; SGLT2 Inhibitor; Tofogliflozin

Introduction

Hyperglycemia is a major manifestation of Type 2 Diabetes Mellitus (T2DM). Sodium-Glucose Co-Transporter 2 (SGLT2) inhibitors are a new class of glucose-lowering drugs that inhibit glucose reabsorption in the renal proximal tubules and excrete glucose into the urine, resulting in lowered blood glucose [1]. The SGLTs inhibitors have been recommended in management of hyperglycemia by the American Diabetes Association and the European Association for the Study of Diabetes [2]. Up to now, six SGLT2 inhibitors were approved in Japan in 2014; ipragliflozin, dapagliflozin, tofogliflozin, canagliflozin, empagliflozin and luseogliflozin that are widely used for the treatment of T2DM [3]. They are used appropriately because the Japanese T2DM patient population has a high proportion of elderly individuals [4]. Shortly after the new launch of SGLT2 inhibitors, safety has become a major concern because of several serious adverse reactions have recognized, including urinary tract infections, ketoacidosis, dehydration and skin disorders [5]. These unfavorable events led to 'Recommendations on appropriate usage of SGLT2 inhibitors' being issued by a committee of Japanese experts in June 2014 [6]. Under these backgrounds, as one of the risk management plans a Post-Marketing Study (PMS) has conducted with the

use of tofogliflozin in elderly patients in routine practice after its launch. The results of the PMS concluded that the incidence of adverse events in elderly patients aged not less than 65 years was similar to that observed in preapproved trials with no additional special concerns [7]. Our previous report showed that electrolyte-imbalance did not occurred during the investigation mainly in 69 elderly patients(the proportion of 65 and over: 77%) receiving tofogliflozin [8]. Several cardiovascular studies have found that SGLT2 inhibitors significantly reduced major adverse cardiovascular events, death and hospitalizations for HF during the treatment with canagliflozin, empagliflozin and dapagliflozin in T2DM patients with complication of CVD [9-11]. Our recent study showed cardiac function characterized by E/e' improved with maintaining homeostasis and also aldsteron value rose in compensation for loss of body fluid within one month after administration of tofogliflozin [12,13]. From these points, it is meaningful to monitoring serum electrolyte and BNP value. SGTL2 inhibitors, including tofogliflozin, acts on proximal tubules and exerts mild osmotic diuresis associated with their mode of action [14]. SGLT2 inhibitors are also known to affect serum electrolyte levels [15]. Although there is potential concern about their effect on electrolyte balance, little is known regarding its effect on electrolyte balance particulary in elderly patients with T2DM.

Therefore, in this research we investigated the efficacy of tofogliflozin in elderly patients with T2DM, and assess its risk of drug-induced electrolyte abnormalities and dehydration.

Patients and Methods

Study Design and Subjects

This is a retrospective study in which subjects were 81 elderly patients, who aged 65 and over, in Kanazawa Medical University Himi Municipal Hospital visited from April 2013 to March 2019, diagnosed as type 2 diabetes mellitus.

Patients received a single 20 mg dose of tofogliflozin daily for 12 months.

Measurements

The efficacy of tofogliflozin was assessed by the change of HbA1c during the 12-month course of the treatment. At month 0, 3, 6 and 12, serum HbA1c, hematocrit, eGFR, BNP, and electrolyte concentration (sodium, potassium, chloride) were measured.

Statistical Analyses

Efficacy of tofogliflozin was assessed by linear regression analyses, using the administration period (months) as an independent variable and HbA1c (%) as a dependent variable.

HbA1c＝b0＋b1×administration period＋e (random error)

The null hypothesis is that slope of the regression curve b1=0.

In the same manner, electrolyte abnormalities and dehydration were also assessed by linear regression analyses, using the concentration of hematocrit, eGFR, BNP, and serum electrolytes (sodium, potassium, and chloride) each as a dependent variable. EZR was used for all the data analyses [16].

Ethical Considerations

This study was conducted in accordance with the guidelines of the Declaration of Helsinki, and was formally approved by the Clinical Research Ethics Committee of Kanazawa Medical University Himi Municipal Hospital.

Results

Demographic data are summarized in Table 1. The total number of patients were 81, 77.50 ±7.75 years old of average age ± standard deviation. Male: They were 30 patients, 77.03±7.11 years old of average ± standard deviation, female: 51 patients, and 79.56±8.34 years old of average age ± standard deviation. The baseline (0 month) value of HbA1c was 7.08±1.00%, and that of hematocrit was 40.19±7.01%. Data were expressed by average ± standard deviation. As anti-diabetic agents, Dipeptidyl Peptidase-4 (DPP-4) inhibitors, sulfonylureas, biguanides, insulins, thiazolidinediones and α-glucosidase inhibitors were administered to 63.8, 25.3%, 19.9%, 14.4%, 2.4%, and 3.8% of the total patients, respectively. No symptomatic hypoglycemic episodes occurred, and no serious adverse events were observed in any of these patients.

n	**81**	
Age (years)	77.5	±7.75
Sex (male/female)	30/51	
HbA1c(%)	7.08	±1.00
Hematocrit(%)	40.19	±7.01
Weight(kg)	56.18	±10.32
Systolic BP(mmHg)	128.84	±20.09
Diastolic BP(mmHg)	70.64	±10.91
Glucose (mg/dL)	170.57	±60.92
Creatinine (mg/dL)	0.83	±0.38
eGFR (mL/min)	64.53	±19.69
BUN (mg/dL)	19.28	±2.59
Anti-diabetic treatment		
DPP-4 inhibitor (%)	54（63.8）	
Sulfonulurea (%)	21（25.3）	
Biguanide (%)	16（19.9）	
Insulin (%)	12（14.4）	
Thiazolidinedione (%)	2（2.4）	
α-Glucosidase Inhibitors(%)	4(3.8)	
Diuretics(%)	16（19.8）	
Antihypersention(%)	70（86.4）	
Antilipdemia%)	27（33.3）	

Table 1: Patient Character Involved.

HbA1c: Hemoglobin A1c; BP: Blood Pressure; LDH: Lactate Dehydrogenase; ALB: Albumin; AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase; TG: Triglyceride; r-GTP: Gamma-Glutamyl Transpeptidase; eGFR: Estimated Glomerular Filtration Rate; BUN: Blood Urea Nitrogen; BNP: Brain Natriuretic Peptide; DPP-4: Dipeptidyl Peptidase-4

Change in HbA1c following administration of tofogliflozin for 12 months is shown in Figure 1. The decrease in HbA1c was significant (p value : <0.01).

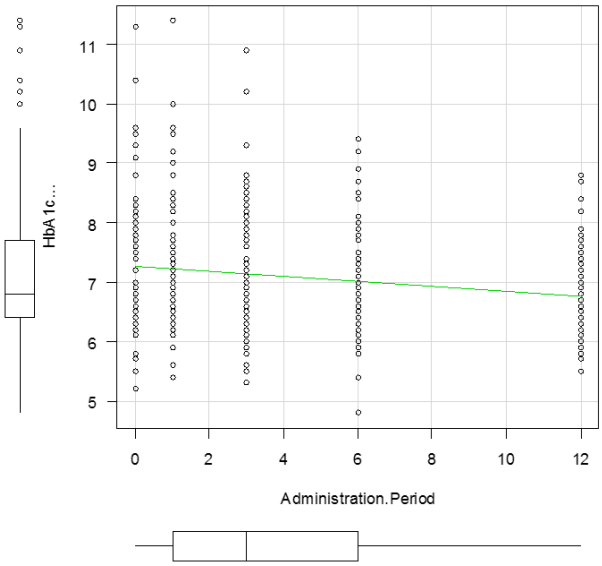

Figure 1: Serum HbA1c vs time profile in elderly patients with T2DM administered tofogliflozin daily for 12 months.

Change in hematocrit following administration of tofogliflozin for 12 months is shown in Figure 2. The change in hematocrit tended to increase (p value: 0.051).

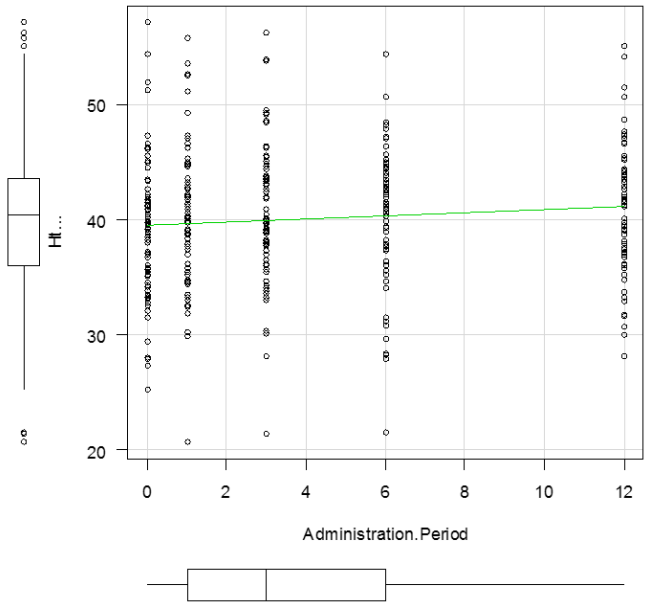

Figure 2: Serum hematocrit vs time profile in elderly patients with T2DM administered tofogliflozin daily for 12 months. The solid lines show linear regression curve.

Change in serum sodium ion concentration following administration of tofogliflozin for 12 months is shown in Figure 3. The increase in sodium was significant (p value : <0.05).

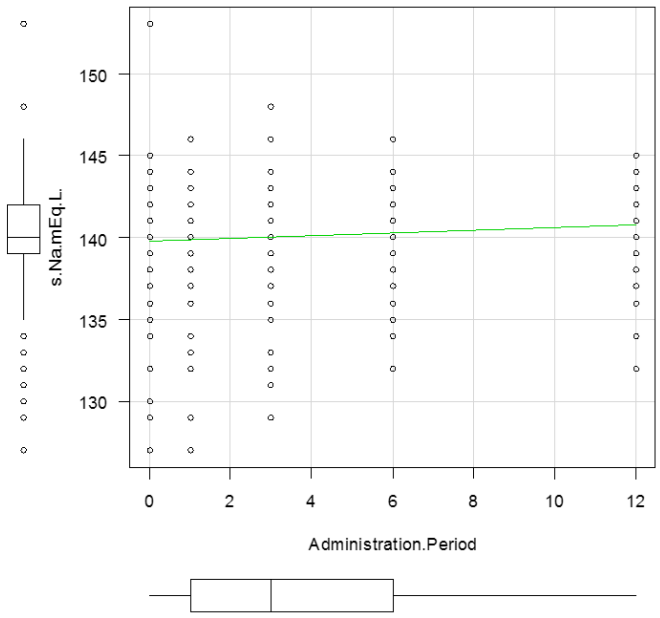

Figure 3: Serum sodium ion concentration vs time profile in elderly patients with T2DM administered tofogliflozin daily for 12 months. The solid lines show linear regression curve.

Change in serum potassium ion concentration following administration of tofogliflozin for 12 months is shown in Figure 4. It is shown that change in potassium ion concentration was not significant (p value: 0.91).

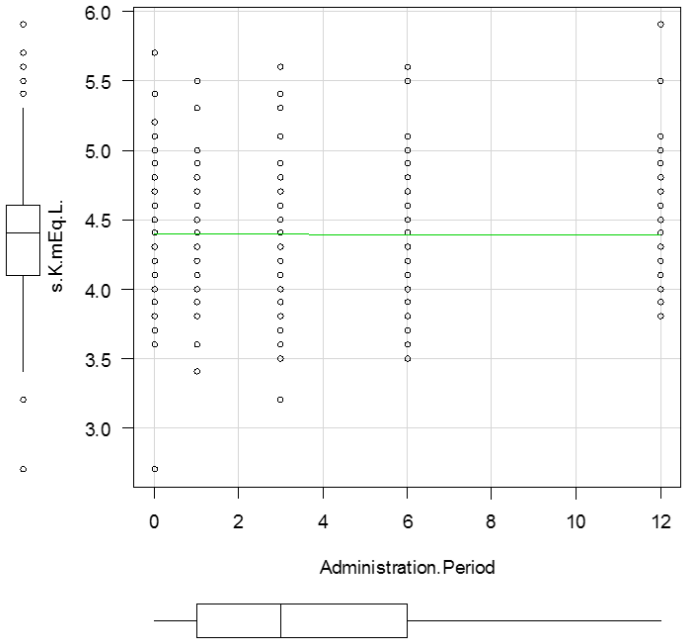

Figure 4: Serum potassium ion concentration vs time profile in elderly patients with T2DM administered tofogliflozin daily for 12 months. The solid lines show linear regression curve.

Change in serum chloride ion concentration following administration of tofogliflozin for 12 months is shown in Figure 5. The increase in chloride ion concentration was significant (p value : <0.01).

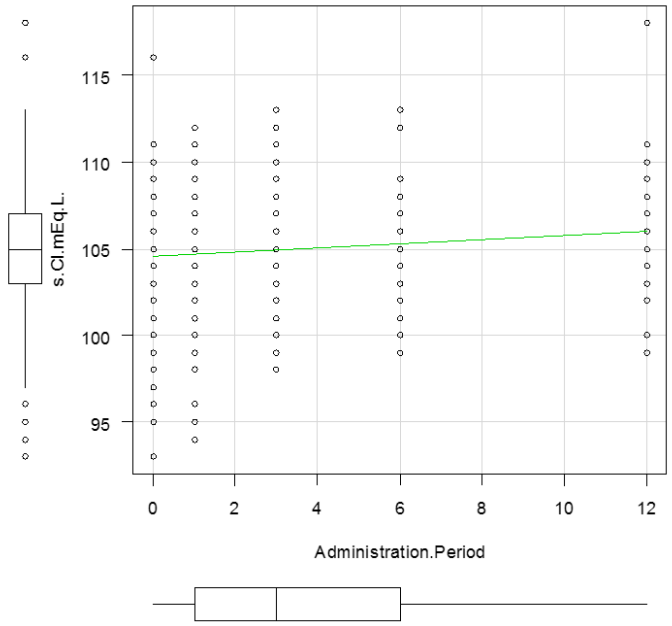

Figure 5: Serum chloride ion concentration vs time profile in elderly patients with T2DM administered tofogliflozin daily for 12 months. The solid lines show linear regression curve.

Change in eGFR following administration of tofogliflozin for 12 months is shown in Figure 6. The increase in eGFR was not significant (p value : 0.31).

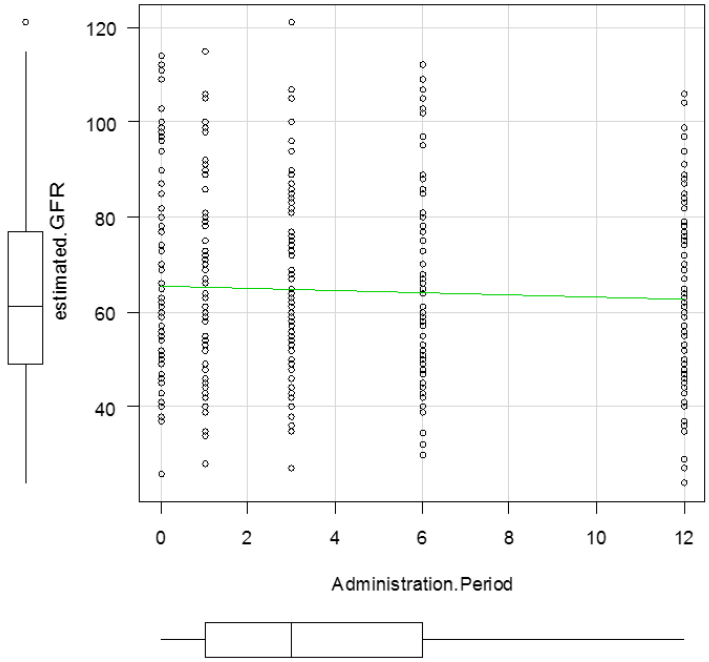

Figure 6: eGFR vs time profile in elderly patients with T2DM administered tofogliflozin daily for 12 months. The solid lines show linear regression curve.

Change in BNP following administration of tofogliflozin for 12 months is shown in Figure 7. The increase in BNP was not significant (p value：0.34).

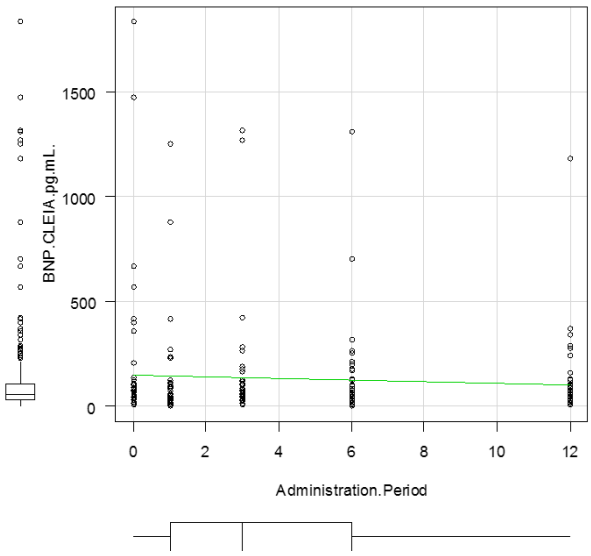

Figure 7: BNP vs time profile in elderly patients with T2DM administered tofogliflozin daily for 12 months. The solid lines show linear regression curve.

Table 2 summarizes parameter estimates of the linear regression analyses. The linear regression model (Y＝b0＋b1×administration period) was applied to each parameter, in which b0 denotes intercept, initial value of these parameters, and b1 denotes slope of the regression curve. These coefficients were determined by the least square method.

Parameter	Coefficient	**Estimates**	**S.E.**	**P-value**
HbA1c (NGSP)	**β0**	**7.26**	**0.14**	**<0.0001***
	β1	**-0.04**	**0.02**	**<0.01**
Ht	**β0**	**39.54**	**0.81**	**<0.0001***
	β1	**0.13**	**0.13**	**0.051**
Na^+	**β0**	**139.78**	**0.43**	**<0.0001***
	β1	**0.07**	**0.07**	**<0.05**
K^+	**β0**	**4.39**	**0.38**	**<0.0001***
	β1	**-0.00**	**0.01**	**0.91**
Cl^-	**β0**	**104.57**	**0.47**	**<0.0001***
	β1	**0.11**	**0.07**	**<0.01**
eGFR	**β0**	**65.54**	**1.51**	**<0.0001***
	β1	**-0.23**	**0.45**	**0.31**
BNP	**β0**	**144.08**	**45.09**	**<0.0001***
	β1	**-3.46**	**7.16**	0.34

Table 2: Parameter estimates of linear regression analyses.

Discussion

The main findings of the current study were summarized in Table 1, which showed significant reduction in HbA1c while serum electrolyte concentration and hematocrit significantly increased within a normal value range., as suggested by regression coefficient b1. This is the first study to elucidate long-term stability of electrolyte concentration in elderly patients with T2DM throughout the course of the 12-month administration of tofogliflozin. Hirose et al., also discovered the stability of serum electrolyte concentration in 20 patients with T2DM during tofogliflozin treatment, although its time course was up to eight weeks [17]. The PMS study of tofogliflozin in Japan found that HbA1c significantly decreased while hematocrit significantly increased. In parallel, the PMS study exhaustively measured various clinical laboratory test results but the study did not measure electrolyte in the blood and/or urine [7]. Administration of tofogliflozin in Japanese patients with T2DM is also known to show some adverse events such as hyperketonemia, ketonuria and pollakiuria [18]. SGLT2 inhibitors are also known to ameliorate body weight, blood pressure, liver function, serum lipids and uric acid, in addition to improvement of glucose metabolism in patients with T2DM [19].

Regarding the effects of SGTL2 inhibitors other than tofogliflozin on electrolyte levels have also been reported. During the 24-week treatment with 10mg of dapagliflozin in patients with T2DM, no clinically relevant changes in serum potassium concentration [20]. SGLT2 inhibitors are known to increase serum concentration of magnesium, potassium and phosphate [15]. Canagliflozin is also known to increase serum magnesium in a dose-dependent manner [21]. Infrequent episodes of potassium elevation occurred with canagliflozin 300 mg, but occurred more often in patients with reduced eGFR [22]. Severe hypercalcemia and hypernatremia have also been reported during the treatment with canagliflozin in patients with T2DM [23]. The change in serum electrolytes levels can be associated with the cardiovascular protection that has been recently reported with empagliflozin and canagliflozin [15]. These results suggest that tofogliflozin could be superior to the other SGLT2 inhibitors in terms of maintaining balance of electrolytes.

Ohara K,et al, reported that SGLT2-Inhibitors do not have a less impact on body fluid composition than furosemide. It is significant body fluid distribution affects cardiac and renal function to resolve the mechanism of preventive acute heart failure [13].

According to chloride theory, an increase in chloride is a compensating change for loss of cellular fluid. Kataoka, et al. reported chloride ion plays a key role as tonicity in regulating body fluid distribution [24]. Showing a slight increase in chloride concentration during observation, results in our study are consistent with this theory. The patients in the present study use other anti-T2DM drugs as combinations. These drugs are known to have no effect on tofogliflozin exposure in healthy male volunteers [25]. SGLT2-Inhibitors improves insulin resistance in human and animal [26-28].

The combination of a SGLT2 inhibitor and a DPP-4 inhibitor is known to be an attractive therapeutic strategy [8]. In conclusion, the 12-month administration of tofogliflozin not only ameliorated glycemic control, with maintaining serum electrolyte concentration stable during the investigation period. BNP is a surrogate marker as clinical index of heart failure. To our best knowledge, there is a few reports regarding BNP in patients receiving SGLT2-inhibitors. In the present study, BNP value did not aggravate in patients receiving tofogliflozin 20mg per day during the observation period. A further study will be expected to find how to assess BNP value in T2DM patients with HFpEF [29].

In addition, tofogliflozin also maintained hemoconcentration without any adverse event of dehydration due to the decrease in circulating plasma volume. Some limitations associated with the present study are the small number of patients involved. This study is a retrospective observational study without any intervention and/or control for use of combination drug, food and fluid intake, that could be confounding factors which can in part interfere interpretation of the causality of tofogliflozin with safety and efficacy profiles. Further analyses will be expected to be stratified by renal, cardiac function, and initial electrolyte value [30].

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