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Original Article

Use of flash glucose monitoring system in assessing safety of the SGLT2 inhibitors during Ramadan fasting in high risk insulin treated patients with type 2 diabetes

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ABSTRACT

Background: The risks of hypoglycemia, dehydration and kidney injury may theoretically be aggravated by people with type 2 diabetes treated with Insulin and SGLT2 inhibitors during Ramadan. Data on safety and efficacy of SGLT2-I in people with type 2 diabetes treated with insulin is scanty. We aimed to assess the impact of SGLT2 inhibitors during Ramadan in high-risk patients with type 2 diabetes treated with insulin, on hypoglycemia, glycemic control and kidney function.

Methods: This is a prospective interventional study on high-risk diabetes patients who insisted on fasting. All patients were treated with insulin ± SGLT2I. All patients received a FGMS and Ramadan focused education. All patients attended clinic before and post Ramadan where they were advised on treatment modification as well as biometric and biochemical measurements.

Results: 95 patients enrolled in the study and 49 of them were on SGLT2i. There was a no significant change in creatinine in both groups. FGMS showed an improvement in the sensor-calculated HbA1c from 7.3 ± 1.5 to 6.8 ± 1.1 and from 8 ± 1.6 to 7.7 ± 1.5 in the SGLT2 group and the non-SGT2i groups, respectively. The hypoglycemia was predominantly reported during Ramadan between 12:00 to 18:00 h, while in pre-Ramadan readings was during 2400–0600 and 1200–1800 slots.

Conclusions: This is the first study that assesses the use of SGLT2i along with insulin during Ramadan, using FGMS in high-risk patients with type 2 diabetes under optimal care. There was minimal interruption of fasting, significant improvement in glycemic control, and no significant change in the kidney function after Ramadan.

1. Introduction

Large epidemiologic studies have shown that fasting Ramadan might increase the risk of hypoglycemia, dehydration and thrombosis in patients with diabetes. This, is frequently coupled with increased risk of post-prandial hyperglycemia with or without diabetic ketoacidosis in those who consume high carbohydrate meals during Ramadan [1]. In order to minimize the potential complications; the IDF-DAR Practical guidelines proposed a risk stratification based on scientific, clinical and practical considerations. The guidelines categorized people with diabetes into three risk groups – very high risk, high risk and moderate/low risk [2]. Patients in very high and high-risk categories are advised not to fast during Ramadan while those in moderate/low risk level can fast, provided that they are empowered by an appropriate education [3]. Despite that, a large proportion of patients with diabetes mellitus and irrespective of their risk, insist on fasting [4,5]. The role of medical professionals is to provide those patients with the appropriated Ramadan-focused education to ensure a safer fasting.

Optimal care during the month of Ramadan has been assessed recently in high risk patients including type 2 diabetes treated with insulin, or those with CKD stage 3 or those with stable coronary artery disease [6–8]. Structured Ramadan-focused education is an essential component of diabetes care during Ramadan. Many studies have proved that education significantly reduce the

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hypoglycemic events and improve glycemic targets during Ramadan [9,10].

Few recent studies have evaluated the CGMs (Continuous glucose monitoring system) and flash glucose monitors system (FGMS) as part of the optimal diabetes care during Ramadan. These new methods helped the patients avoid the frequent finger pricks self-glucose monitoring, and provide semi-continuous information on glucose levels. Despite improved glycemic control on CGMs, the accuracy of these sensors at the extremes of the glycemic ranges (Severe hypoglycemia and severe hyperglycemia) remains controversial [11–13].

Many trials have evaluated the safety of different AHAs (Anti-hyperglycemic agents) as part of optimal diabetes care during the month of Ramadan [13–26]. The results of these trials were variable. Over the last few years, the SGLT2i (Sodium Glucose co-transporter 2 inhibitors) were used widely in many countries given their cardiovascular benefits. The main concerns related to the use of the SGLT2i during Ramadan was the theoretical risk of osmotic diuresis-induced hypovolemia and dehydration, which, hypothetically, may increase the risk of acute kidney injury [27]. When compared to SU (Sulphonylurea), the SGLT2i were associated with significantly lower risk of hypoglycemia and hypovolemia [28,29]. Though DKA and renal compromise with SGLT2i are reported outside Ramadan, they have not been reported to be a problem during Ramadan. In a real-world evidence study, the use of SGLT2i on top of other OHA with or without insulin, the SGLT2-i increases the risk of hypoglycemia during Ramadan when it is combined with insulin, and the kidney function remained stable [30].

The current study is a unique one compared to all previous studies which were done to assess the safety of different AHAs in Ramadan, since it is the first study that particularly included patients with diabetes at high risk of fasting. Moreover, all patients were on insulin for at least three months before Ramadan. Furthermore, this would be the first study in patients with type 2 diabetes on SGLT2i and insulin to use FGMS technology. The use of the sensor allowed a more in-depth view of hyperglycemia as well as the frequency, duration, and severity of hypoglycemia before, during, and after Ramadan.

2. Patients and methods

This is a sub-analysis of a prospective interventional single-centered trial conducted at Dubai Health authority (DHA), the main government sector in the emirate of Dubai, UAE. Recruitment and completion of data collection was in 2016. The study was approved by the local research ethics committee and was funded by a grant from Al-Jalila Foundation, UAE. We counselled all the patient with diabetes who were categorized as at high risk of fasting (as per the IDF/DAR risk stratification scale [1], who insisted on fasting despite the medical advice.

We included data of patients 18–75 years of age, with a known diagnosis of type 2 diabetes mellitus, who are were all using insulin. Some patients were concurrent renal disease (CKD stage 3) or history of ischemic heart disease. All patients were selected at convenience 1–2 months before Ramadan, counselled, and asked to sign an informed consent. Pregnant ladies and patients with T1DM were excluded from this study.

2.1. General aim of the study

To assess the safety of the SGLT2 inhibitors use during Ramadan in high risk patients with diabetes.

2.2. Primary objectives

To compare the changes in biometric parameters (blood pressure and weight) as well as biochemical changes (glycemic control, lipids profile and renal function) before and after Ramadan in people with diabetes considered as high risk of fasting, with or without SGLT2i.

2.3. Secondary objectives

- To assess the incidences, duration and severity of hypoglycemia before and during Ramadan, using the FGMS.
- To compare the risk of hospitalization, frequency of breaking the fast (due to hypo or hyperglycemia), number of days fasted in both groups

3. Procedure

The study was conducted 4–6 weeks before Ramadan to 2–4 weeks after Ramadan. The study flown through three phases, phase 1 (4–6 weeks before Ramadan) for counselling, education, and doses adjustment. Second phase (during Ramadan) for followup of adherence, trouble shooting, and the third phase (2–4 weeks after Ramadan) for completion of the study and any further medications alterations (Fig. 1).

We screened all patients with diabetes 4–6 weeks before Ramadan. Those who decided to fast were provided with 90 min Ramadan focused education to empower them about the diabetes management during Ramadan (Phase 1). Moreover, the session also covered the Freestyle Libre sensor installation techniques, functionalities of the flash glucose monitoring device and trouble-shooting tips.

During the same visit, all patients did the basic investigations (HbA1c, Creatinine, Urea and electrolytes, eGFR, lipids profile) and received a freestyle libre device and sensors. A 24-h hot line was established to help the patients applying the study protocol, and equally to aid them in having a safer fasting.

During last 10 days of Ramadan (Phase 2), patients were advised to attend at least one diabetes or diabetes educator clinic, in order to download the sensor data, and to supply them with the second and third libre sensor. During Ramadan, all patients received a telephone call to reinforce the education points on breaking fasting and dose adjustment if required.

Two to four weeks after Ramadan (phase 3), all participants were seen in the clinic and had their biometric and biochemical parameters rechecked. In this analysis, we have compared patients on SGLT2i on top of insulins + OHAs versus patients on insulins + OHAs (other than SGLT2i). Both groups were patients with T2DM on insulin. Some were also with either CKD stage 3 or history of ischemic heart disease or. The comparison parameters included biometric, biochemical changes before and after Ramadan, as well as the FGMS data on glycemic indices before and during Ramadan days.

4. Ethical approvals

The study has been approved by the ethical committee of Dubai Health authority.

5. Funding

This study was funded by a grant from Al-Jalila foundation of Dubai – UAE.

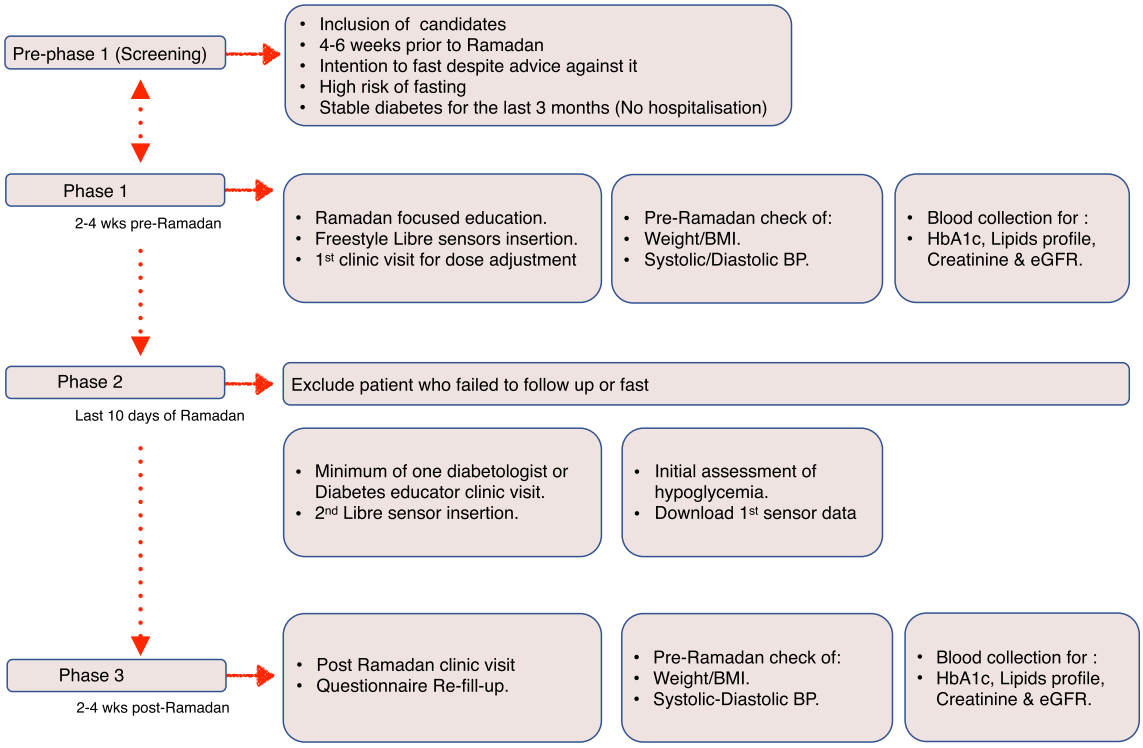

Fig. 1. The methodology and the study flow.

6. Data collection and analysis

All data was then entered in an excel sheet and was prepared for analysis. Paired Student's t-tests were used to test the significance of differences between values for continuous variables measured at baseline and at various time points. Independent *t*-test, one-way analysis of variance (ANOVA) and Chi square (x2) test were used to assess the significance of differences between the groups. Continuous data are presented as the mean ± standard deviation (SD), and categorical data are presented as frequencies and percentages. Differences with P-values ≤ 0.05 were considered to be statistically significant. Analyses were performed using Statistical Package for the Social Sciences (SPSS) version 23 (IBM Corp, New York, USA).

7. Results

Total of 95 patients were included in this study. All of them were patients with diabetes at high risk of complications if considered fasting Ramadan (T2DM on insulin, T2DM with CKD stage 3 or history of IHD), all patients received FGMS pre-Ramadan and during Ramadan.

The patients were divided into two groups, T2DM patients on SGLT2i on top of insulin + OHAs will be referred to as SGLT2i group (n = 49). While the control group was T2DM patients with insulin + OHAs (excluding SGLT2i), this will be referred to as Non-SGLT2i group (n = 46).

Majority of participants were females in both groups. Approximately 44.8% (n = 22) of the SGLT2i group were on sulphonylurea (SU), compared to only 28.2% (n = 13) in the Non-SGLT2i group (Table 1).

Biometric data before and after Ramadan in both groups showed a numerical reduction in the weight and a mild elevation of systolic and diastolic BP (Table 2). None of these biometric changes was statistically significant. However, biochemical results showed a significant improvement in glycemic control from 7.95 ± 1.1 to 7.6 ± 1.1% (p = 0.028) in SGLT2i group, and non-significant reduction in the non-SGLT2i groups from 7.7 ± 1.0 to 7.6 + 1.0 (p = 0.56) before and after Ramadan. (Table 2). Serum creatinine showed non-significant numerical improvement in the SGLT2i groups from 0.8 ± 0.2 to 0.7 ± 0.2 mg/dl (p = 0.85), while, there was no change in the comparator group before and after Ramadan. There were no significant changes in lipids panel in both groups (Table 2). There was no diabetic ketoacidosis (DKA) reported during the whole study period.

7.1. Flash glucose monitoring system data

Upon comparing the continuous glucose assessment before and during Ramadan there was an improvement in the sensor-calculated HbA1c from 7.3 ± 1.5 to 6.8 ± 1.1 and from 8 ± 1.6 to 7.7 ± 1.5 in the SGLT2 group and the non-SGT2i groups, respectively compared to the pre-Ramadan levels. The average glucose improved from before Ramadan to during Ramadan in the SGLT2 group from 155 + 41 to 151.3 + 34.9, while in the non SGLT2 group it dropped from 187 + 47.8 to 182 + 59 (Table 3).

At baseline (pre-Ramadan), there was higher numbers of hypoglycemic episodes as well as duration of hypoglycemia in SGLT2i group compared the control group. In both groups, hypoglycemic episodes were reduced in number and in duration during Ramadan. The reduction in hypoglycemia duration in SGLT2I group was much more than the control group. However, there was no statistical difference between both groups in these parameters (Table 3). Moreover, there was no significant difference in both groups in terms of severity of hypoglycemia neither before nor during Ramadan (Table 3).

The timing of hypoglycemia in SGLT2i group showed an increase during 1200–1800 and at the same time reduction in all other

Table 1
Baseline characteristics and the study population.

Variable	SGLT2i group Median + SD/n (%)	Non-SGLT2 group Median + SD/n (%)
Number of patients	49	46
Age	57.5 + 9.1	55.4 + 9.4
Males	19 (34.8%)	16 (38.8%)
Females	30 (65.2%)	30 (61.2%)
Number of patients on Sulphonylurea	22 (44.8%)	13 (28.2%)
Number of Hypoglycemia with symptoms during Ramadan	8 (16.3%)	20 (43.4%)
Number of Severe hypoglycemia during Ramadan	0	0
N Number of days fasted in Ramadan	29.0 + 1	28.5 + 1
Number of days broke the fast	8 (16.3%)	7 (15.2%)

Table 2
Comparison of biometric and biochemical variable before and after Ramadan in SGLT2i versus the Non-SGLT2i groups before and after Ramadan.

Variable	SGLT2i group (Median + SD)			Non-SGLT2i group (Median + SD)		
	BR	AR	P Value	BR	AR	P Value
Weight (Kg)	82 ± 13.9	81.9 ± 15.5	0.84	85 ± 11.1	83 ± 12.1	0.93
HbA1c (%)	7.95 ± 1.1	7.6 ± 1.1	**0.028**	7.7 ± 1.0	7.6 ± 1.0	0.56
SBP (mmHg)	131 ± 17.1	135 ± 15.4	0.49	122.5 ± 17.8	124 ± 16.1	0.78
DBP (mmHg)	70 ± 10.6	71 ± 8.9	0.50	71.5 ± 9.4	72 ± 10.5	0.79
LDL (mg/dl)	88 ± 29.9	89 ± 26.3	0.59	83 ± 32.1	88 ± 31.6	0.78
TG (mg/dl)	117.5 ± 93.2	125 ± 72.0	0.57	113.5 ± 42.0	109.5 ± 76.9	0.73
TC (mg/dl)	174 ± 35.7	167.5 ± 34.5	0.63	157 ± 40.0	164.5 ± 39.9	0.18
HDL (mg/dl)	48.5 ± 13.5	48.5 ± 14.6	0.50	49.5 ± 19.6	48 ± 16.0	0.61
Creatinine (mg/dl)	0.8 ± 0.2	0.7 ± 0.2	0.85	0.7 ± 0.2	0.7 ± 0.2	1.00
eGFR (mg/ml/1.73m^2)	100.5 ± 21.4	99 ± 16.8	0.97	101.9 ± 16.4	97.8 ± 16.2	0.75

Table 3
Comparison of FGMS data before and during Ramadan in SGLT2i versus the Non-SGLT2i groups before and during Ramadan.

Variable		SGLT2i group	Non-SGLT2 group	P value
HbA1c BR (%)		7.3 ± 1.5	8 ± 1.6	0.12
HbA1c During Ramadan (%)		6.8 ± 1.1	7.7 ± 1.5	**0.05**
Number of hypoglycemic events BR (n/Sensor)		5 ± 6.9	4.3 ± 5.3	0.87
Number of hypoglycemic events During Ramadan (n/Sensor)		3.9 ± 5.1	3.3 ± 3.8	0.97
Duration of hypoglycemia BR (minutes)		89.5 ± 80.7	73.2 ± 69.9	0.46
Duration of hypoglycemia During Ramadan (minutes)		62.8 ± 68.5	68 ± 84.6	0.95
Severity of hypoglycemia BR (mg/dl)	<50	1.2 ± 2	1.2 ± 1.9	0.89
	50–60	1.7 ± 2.7	1.3 ± 2	0.59
	60–70	2.2 ± 3.3	1.8 ± 2.5	0.91
Severity of hypoglycemia During Ramadan (mg/dl)	<50	1 ± 2.3	0.8 ± 1.6	0.74
	50–60	1.3 ± 2	1 ± 1.3	0.85
	60–70	1.6 ± 2.2	1.4 ± 2.3	0.92
Average glucose BR (mg/dl)		155 ± 41	187 ± 47.8	**0.00**
Average glucose During Ramadan (mg/dl)		151.3 ± 34.9	182 ± 59	**0.045**

times during Ramadan compared to pre-Ramadan. The Non-SGLT2i group showed mild or no change in hypoglycemia at different time slots of the day between Ramadan and pre-Ramadan. None of these differences was statistically significant (Table 4). During Ramadan, the incidences of hypoglycemia were comparable between the two groups, except between 1200 and 1800 h was 2.3 + 3.8 and 1 + 1.9 in the SGLT2i and the Non-SGLT2i groups respectively (p = 0.59).

Table 4
Comparison of hypoglycemia incidences at different time slots within the day before and during Ramadan in SGLT2i versus the Non-SGLT2i groups.

Variable	Frequency of hypoglycemia at different time slots of the day (n ± SD)			
Before Ramadan	2400–0600	0600–1200	1200–1800	1800–2400
SGLT2i group	1.6 ± 2.2	1.1 ± 2.2	1.5 ± 2.1	0.9 ± 1.7
Non-SGLT2 group	1.4 ± 1.8	0.9 ± 1.3	1.3 ± 2	0.8 ± 1.4
P Value	0.99	0.9	0.39	0.99
During Ramadan	**2400–0600**	**0600–1200**	**1200–1800**	**1800–2400**
SGLT2i group	0.6 ± 1.1	0.6 ± 1.3	2.3 ± 3.8	0.5 ± 0.8
Non-SGLT2 group	1 ± 1.3	0.4 ± 1	1 ± 1.9	0.8 ± 1.3
P Value	0.34	0.87	0.59	0.26

8. Discussion

The current study is the first study that used FGMS in high-risk patients with diabetes were treated with insulin and SGLT-2i who observed Ramadan fasting. The current study observed not only the glycemic changes through FGMS, but also other different parameters like tolerability to complete the fast and biochemical parameters including renal functions, BP and weight before and after Ramadan.

The first study done for the safety of SGLT-2i in Ramadan was in 2016 from Malaysia by Wan Seman et al. [28]. Seman et al. reported a lower risk of hypoglycemia in the Dapagliflozin group. Similarly, The CRATOS, a sizeable multicenter observation study conducted in different Middle Eastern countries also observed the safety of

Canagliflozin versus SU during Ramadan of 2016 [28]. The results of this study likewise showed less incidence of both symptomatic and documented hypoglycemia in Canagliflozin group compared to the SU group. The cohort of patients in both studies was a relatively a lower risk group as none of the patients were on insulin and all patients had normal eGFR. These finding are in line with our data that showed much higher numerical reduction in the SGLT2i group compared to non-SGLT2i group during Ramadan compared to pre-Ramadan. This occurred despite the SGLTi group had 44.8% patients on SU compared to 28.2% patients in the non-SGLT2i. Moreover, our study patients are a higher risk group as they were all on insulin, with longer duration of diabetes and included some patients with CKD stage 3 or stable coronary heart disease.

Both severity and duration of hypoglycemia reduced during the month of Ramadan. However, the SGLT2i group had shorter and less severe episodes in comparison to the non-SGLT2i group (62.8 ± 68.5 vs 68 ± 84.6, p 0.95). This could have been partly explained by a possible Pre-Ramadan dose adjustment by the treating physicians as well as the personal self-titration after having Ramadan focused education.

Among the biophysical and biochemical parameters, there is no significant alteration in weight and lipid profile. However, HbA1c showed significant reduction in the SGLT2 group than non-SGT2i groups. This improvement is unequivocally seen in all the prior studies done to assess the safety of SGLT-2i in Ramadan to date [28–30]. This glycemic improvement by the end of Ramadan could be multifactorial. Patient education, FGMS and pre-Ramadan clinic visit could have collectively played a role in that.

The non-significant modest improvement in serum creatinine in the SGLT2i groups from 0.8 ± 0.2 to 0.7 ± 0.2 mg/dl ($p = 0.85$) is reassuring. Bearing in mind that all patients in our cohort are at high risk of fasting, with some of them with CKD-stage 3 or IHD and all of them were on insulin therapy. All our patients received Ramadan-focused education including adequate hydration and to report any excessive thirst. Indeed, the mean fasting days was 29 days in the SGLT2i group which reflects the ability of this group of patients to tolerate SGLT2i therapy despite their treatment with insulin and the moderate renal impairment or IHD present in some of them. This is of particular interest in view of the recent guidelines of use of SGLT2i in patients with previous IHD and or renal disease as none of these studies were done on patients observing Ramadan fasting [31,32].

A recent study from Singapore assessed patients on stable dose of SGLT2i and compared them with patients on standard of care, the eGFR cut off was> 45 mg/ml/1.73 m^2 [33]. The aim was to assess the biometric and biochemical changes including the serum ketone changes during Ramadan. SGLT2i treated group had a non-significant mean change of the B-hydroxybutyrate levels during Ramadan compared to the standard of care group (mean change of −0.01 versus −0.02 mmol/L, $p = 0.649$). The mean change in the eGFR was ±6.0 versus ±4.2 ml/min/1.73 m^2, $p = 0.399$ in SGLT2i and the nonSGLT2i, respectively. The authors concluded that the use of SGLT2i during Ramadan did not increase risk of ketonemia, renal jeopardy and dehydration as compared to those patients not on SGLT2 inhibitor [33]. Similarly, none of our patients were admitted to hospital for any medical reason.

9. Conclusion

This is the first study that assesses the use of SGLT2i along with insulin during Ramadan, using FGMS in high-risk patients with type 2 diabetes under optimal care. In patients with diabetes on insulin, the use of SGLT2i was associated with minimal interruption of fasting, significant improvement in glycemic control, and no significant change in the kidney function after Ramadan. Under optimal diabetes care, using SGLT2i in patients in patients at high risk of fasting did not significantly increase the rate or severity of hypoglycemia, hospitalization, plasma volume related jeopardies or worsening in renal function.

10. Significance of the study

This is the first study that addressed the use of SGLT-2i in patients for high risk of Ramadan fasting including patients with CKD stage 3, IHD, and insulin treatment. Conventionally many physicians choose either avoiding initiation or, sometimes, stopping a current SGLT-2i before Ramadan due to the hypothetical potential risk of renal injury and hypovolemia. Nonetheless, our study might have reflected the value of proper Ramadan-focused diabetes education, close monitoring of glycemic fluctuation using the technology of the FGMS, in attaining a safer Ramadan fasting in such high risk fasting group.

Conflicts of interest

All authors confirm no conflict of interest. The study was funded by a grant from Al Jalila Foundation – Dubai – UAE, grant documents are available on request.

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