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The association between vitamin D levels and heart rate variability in patients with type 2 diabetes mellitus

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Abstract

To assess the association between serum vitamin D levels and heart rate variability in patients with type 2 diabetes mellitus (T2DM). This study included 469 patients who were retrospective assessed for eligibility from Changzhou Second People's Hospital, Affiliated Nanjing Medical University, between March 2013 and June 2020. A total of 191 T2DM patients were recruited and divided into 3 groups. A total of 191 patients were recruited. A significant difference was noted among groups for HbA1c ($P < .001$), serum uric acid ($P = .048$), and urea nitrogen ($P = .043$). The Vitamin D level in deficiency, insufficiency, and sufficient was 23.17, 38.89, and 63.01 nmol/L, respectively. The insufficient group had lower levels of percentage of normal-to-normal intervals differing by more than 50 milliseconds, and the square root of the mean of the squares of the differences between adjacent normal-to-normal R peak-to-R-peak time intervals than the sufficient vitamin D group. Furthermore, patients in deficiency and insufficiency group were associated with high level of low frequency power/high frequency power as compared with sufficient vitamin D group. Finally, serum 25-hydroxyvitamin D (25(OH)D) levels were positively correlated with rMSSD ($P = .002$). This study found that low serum 25(OH)D levels were associated with reduced heart rate variability parameters in patients with T2DM.

Abbreviations: CAN = cardiac autonomic neuropathy, ECG = electrocardiogram, HDL-C = high-density lipoprotein cholesterol, HF = frequency power, HRV = heart rate variability, LDL-C = low-density lipoprotein cholesterol, MD = mean difference, SDNN = standard deviations of all normal-to-normal intervals, T2DM = type 2 diabetes mellitus, TC = cholesterol, TG = triglycerides, UA = uric acid, VDR = vitamin D receptors.

Keywords: cardiac autonomic neuropathy, cardiovascular disease, diabetic complication, heart rate variability, type 2 diabetes mellitus, vitamin D

1. Introduction

The prevalence of diabetes mellitus has been increasing worldwide. It is estimated that in 2017 there were 451 million people with diabetes worldwide, and these figures are expected to increase by up to 693 million by 2045.[1] Type 2 DM (T2DM) is frequently associated with severe complications, including disability, cardiovascular disease, and cancer at various sites.[2–4] A previous study reported that cardiac autonomic neuropathy (CAN) was a common event but often overlooked complication in diabetic patients, which was significantly associated with an increased risk of cardiovascular morbidity and mortality.[5] Another study has demonstrated that CAN plays an important role in cardiac arrhythmias and sudden cardiac death.[6] However, numerous diabetic patients with CAN were asymptomatic before the onset of cardiovascular disease. Currently, the most reliable approach for assessing CAN is based on heart rate variability (HRV), which is considered as a non-invasive approach to measuring cardiac autonomic regulation.[7,8] The HRV measurement was obtained through the analysis of time variations between heartbeats, known as R peak-to-R-peak time (RR) intervals of the electrocardiogram.[9]

Nowadays, vitamin D has already been demonstrated to play a critical role in the regulation of bone health physiology and calcium-phosphorus homeostasis by acting at the level of skeletal bone, intestine, and kidney.[10] Vitamin D receptors (VDR) have been detected in several other tissues, including the heart, brain, and blood vessels, and a growing body of evidence focuses on the extra-skeletal benefits of vitamin D. Numerous studies have addressed the role of vitamin D deficiency on the risk of cardiovascular morbidity and mortality.[11,12] However,

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All data generated or analyzed during this study are included in this published article [and its supplementary information files]. The data generated in this study are available within the article and its supplementary data files. Further inquiries can be directed to the corresponding author.

The Ethics Committee of Changzhou Second People's Hospital, Affiliated Nanjing Medical University approved this study. Informed consent was obtained from all subjects involved in the study.

This study was carried out in accordance with the declaration of Helsinki.

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few studies have addressed the role of vitamin D levels on HRV parameters in patients with T2DM. This study aimed to assess the association of serum vitamin D levels with HRV parameters in T2DM patients.

2. Materials and Methods

2.1. Study subjects

The Ethics Committee of Changzhou Second People's Hospital, Affiliated Nanjing Medical University approved this study ([2020] KY021-01). Informed consent was obtained from all individual participants included in the study. This study was a cross-sectional study, containing 469 patients retrospectively assessed for eligibility from Department of Endocrinology in Changzhou Second People's Hospital, Affiliated Nanjing Medical University, between March 2013 and June 2020. The demographic, biochemical, and clinical data were abstracted from the electronic medical record system. The diagnostic criteria for T2DM patients were based on the World Health Organization criteria. Then 278 patients were excluded and 191 patients were included based on exclusion criteria. The exclusion criteria were as follows: the vitamin D data were not available; patients without T2DM; regular administration of calcium or vitamin D supplements within the previous 3 months (except for durations less than 1 week), beta-blocker treatment, antianxiety, or tricyclic antidepressant treatment; acute complications, including diabetic ketoacidosis, hyperglycemic, hyperosmolar states, previous acute myocardial infarction, cardiac surgery, emergency cardiac intervention operation, other endocrine disorders, severe infection, severe hepatosis and renal dysfunction, and other reasons, including information regarding HRV was absent. Patients were divided into 3 groups: deficiency [25-hydroxyvitamin D (25(OH)D) < 30 nmol/L], insufficiency [30 nmol/L ≤ 25(OH)D < 50 nmol/L], and sufficiency [25(OH)D ≥ 50 nmol/L] on the basis of Chinese guidelines.[13]

2.2. Physical and biochemical measurements

Body mass index (BMI) was calculated as weight (in kilograms), divided by the square of height (in meters), and weight (kg) and height (cm) were measured to the nearest 0.5 kg and 1.0 cm. The enzymatic method with an automatic biochemical analyzer (Siemens Advia 2400, Munich, Germany) was applied to measure the serum uric acid (UA), urea nitrogen, serum creatinine, total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C). Moreover, a chemiluminescence system (Roche, Basel, Switzerland) was employed to measure C-peptide, and glycated hemoglobin (HbA1c) concentration was measured by ion-exchange high-performance liquid chromatography (TOSOH HLC-723G8, Tokyo, Japan). Finally, the serum 25(OH)D concentration was assessed using an enzyme-linked immunosorbent assay (Guangzhou PHICON Biotech, Guangzhou, China).[14]

2.3. HRV measurements

Ambulatory electrocardiogram monitoring was performed for 24 hours to access the cardiovascular autonomic modulation during normal day-time activities, night-time, and sleep, by using a portable Holter recorder (Seer Light, GE, American, General Electric Company, Boston, Massachusetts, United States). HRV analysis was performed with a MARS system and the parameters in HRV, including standard deviations of all normal-to-normal intervals (SDNN), mean of the standard deviations of normal-to-normal intervals in all 5-minute segments of the entire recording (ASDNN), percentage of normal-to-normal intervals differing by more than 50 milliseconds (pNN50), low frequency power (LF), high frequency power (HF), LF/HF, standard deviation of the consecutive 5-minute averages of normal-to-normal intervals (SDANN), and the square root of the mean of the squares of the differences between adjacent normal-to-normal RR intervals (rMSSD).

2.4. Statistical analysis

Sample size estimated according to the differences of HRV among groups and type I error, and according to the study conducted by Mann et al.[15] The values of continuous variables were reported as mean ± standard deviation if they met normal distribution. The 1-way analysis of variance (ANOVA) was applied to assess the differences among all groups for patients' characteristics. The chi-square test was used to compare the categorical variables. The Least-Significant Difference mean difference (MD) was used to compare the mean difference of HRV parameters among all groups. Multivariate linear regression analyses were used to explore the correlations between the serum 25(OH)D and HRV parameters, using the stepwise variables selection. *P* value for inclusion and exclusion were .05 and .10, respectively. All reported *P* values were 2-sided, and a *P* value of less than .05 was considered statistically significant. All statistical analyses were conducted using IBM SPSS Statistics for Windows, version 19.0 (SPSS 19.0, International Business Machines Corporation, Armonk, New York, United States). This study was reviewed by Xin-Hua Ye from Nanjing Medical University.

3. Results

3.1. Characteristics of study subjects

The characteristics of the recruited T2DM patients are summarized in Table 1. A total of 191 patients were included, containing 96 males (50.26%) and 95 females (49.74%), and the mean age of patients was 59.75 ± 10.78 years. A significant difference was noted among groups for HbA1c (*P* < .001), serum UA (*P* = .048), and urea nitrogen (*P* = .043), while there were no significant differences among groups for age, percent male, systolic blood pressure, diastolic blood pressure, hypertension, height, weight, BMI, C-peptide (fasting), serum creatinine, TC, TG, HDL-C, and LDL-C.

3.2. HRV parameters according to the status of vitamin D

The comparisons of HRV parameters based on the vitamin D status are shown in Table 2. First, we noted that patients in the deficiency group were associated with lower SDNN (MD: −14.69; 95% CI: −25.68 to −3.71), ASDNN (MD: −7.88; 95% CI: −13.85 to −1.90), pNN50 (MD: −5.24; 95% CI: −8.19 to −2.29), LF (MD: −2.70; 95% CI: −5.37 to −0.03), HF (MD: −3.09; 95% CI: −5.02 to −1.17), SDANN (MD: −11.81; 95% CI: −22.15 to −1.48), and rMSSD (MD: −7.73; 95% CI: −12.12 to −3.34), when compared with those of patients in the sufficiency group. Second, patients in the insufficiency group were associated with lower pNN50 (MD: −3.20; 95% CI: −5.88 to −0.52), and rMSSD (MD: −4.62; 95% CI: −8.60 to −0.63). Third, Patients in the deficiency group (MD: 0.19; 95% CI: 0.03 to 0.35) and insufficiency group (MD: 0.15; 95% CI: 0.00–0.29) were associated with elevated LF/HF than those in sufficiency group. Finally, there was no significant difference between the insufficiency group and the sufficiency group for SDNN, ASDNN, LF, HF, and SDANN.

3.3. Association of serum 25(OH)D levels with HRV parameters

The associations between serum 25(OH)D levels with HRV parameters are displayed in Table 3. The univariate linear regression analysis indicated the level of 25(OH)D was significantly related to HF (*P* = .031). Moreover, the multivariate

Table 1

Characteristics of patients according to vitamin status.

Index	All	Vitamin D status			*P* value
		Deficiency, (n = 55)	Insufficiency, (n = 89)	Sufficiency, (n = 47)	
Age (yr)	59.75 (10.78)	60.44 (11.72)	57.92 (9.83)	62.43 (10.96)	.058
Male, n (%)	96 (50.26)	22 (40.00)	48 (53.93)	26 (55.32)	.194
Systolic blood pressure (mm Hg)	136.91 (17.61)	138.75 (19.74)	136.90 (17.32)	134.79 (15.51)	.530
Diastolic blood pressure (mm Hg)	81.80 (10.41)	81.05 (10.40)	82.81 (10.94)	80.74 (9.37)	.451
Hypertension, n (%)	74 (38.74)	25 (45.45)	34 (38.20)	15 (31.91)	.372
Height (cm)	164.72 (7.88)	163.75 (7.98)	165.15 (7.71)	165.06 (8.13)	.553
Weight (kg)	68.19 (11.90)	66.24 (13.11)	69.43 (10.94)	68.14 (12.09)	.295
Body mass index (kg/m^2)	25.06 (3.52)	24.65 (4.02)	25.40 (3.31)	24.92 (3.28)	.439
HbA1c (%)	9.03 (2.15)	9.88 (2.38)	8.88 (2.02)	8.34 (1.78)	<.001
C-peptide (fasting) (ng/mL)	2.02 (1.20)	1.72 (1.10)	2.15 (1.16)	2.11 (1.33)	.091
Serum uric acid (μmol/L)	297.87 (86.89)	273.73 (90.69)	306.16 (89.42)	310.42 (72.39)	.048
Urea nitrogen (mmol/L)	5.89 (1.45)	5.56 (1.33)	5.88 (1.45)	6.28 (1.53)	.043
Serum creatinine (μmol/L)	74.37 (17.96)	71.66 (18.28)	76.79 (17.36)	72.95 (18.48)	.207
Total cholesterol (mmol/L)	4.62 (1.15)	4.78 (1.29)	4.66 (1.17)	4.36 (0.88)	.164
Triglycerides (mmol/L)	2.18 (2.98)	2.37 (3.91)	2.17 (2.99)	1.98 (1.29)	.804
HDL-C (mmol/L)	1.30 (0.51)	1.31 (0.40)	1.35 (0.64)	1.22 (0.31)	.369
LDL-C (mmol/L)	2.55 (0.77)	2.65 (0.77)	2.58 (0.80)	2.39 (0.68)	.194

HbA1c = glycated hemoglobin, HDL-C = high density lipoprotein-cholesterol, LDL-C = low density lipoprotein-cholesterol.

Table 2

HRV parameters of patients according to the vitamin D status.

Index	Deficiency, (n = 55)	Insufficiency, (n = 89)	Sufficiency, (n = 47)	*P* value	LSD MD	
					Deficiency vs sufficiency	Insufficiency vs sufficiency
Vitamin D (nmol/L)	23.17 (4.87)	38.89 (6.02)	63.01 (12.05)	<.001	−39.85 (−42.86 to −36.83)*	−24.12 (−26.86 to −21.38)*
SDNN (ms)	101.31 (26.72)	114.61 (27.79)	116.00 (29.95)	.010	−14.69 (−25.68 to −3.71)*	−1.39 (−11.37 to 8.58)
ASDNN	40.65 (14.44)	46.33 (14.46)	48.53 (17.46)	.024	−7.88 (−13.85 to −1.90)*	−2.21 (−7.63 to 3.22)
pNN50 (%)	3.68 (5.19)	5.73 (7.03)	8.93 (10.27)	.003	−5.24 (−8.19 to −2.29)*	−3.20 (−5.88 to −0.52)*
LF	13.24 (6.58)	15.23 (6.29)	15.94 (7.94)	.106	−2.70 (−5.37 to −0.03)*	−0.71 (−3.13 to 1.71)
HF	8.69 (4.61)	10.14 (4.40)	11.78 (6.06)	.008	−3.09 (−5.02 to −1.17)*	−1.64 (−3.39 to 0.10)
LF/HF	1.59 (0.42)	1.55 (0.42)	1.40 (0.38)	.057	0.19 (0.03 to 0.35)*	0.15 (0.00 to 0.29)*
SDANN	90.15 (26.50)	102.42 (25.84)	101.96 (27.22)	.018	−11.81 (−22.15 to −1.48)*	0.46 (−8.92 to 9.84)
rMSSD	21.67 (9.19)	24.79 (10.23)	29.40 (14.61)	.003	−7.73 (−12.12 to −3.34)*	−4.62 (−8.60 to −0.63)*

ASDNN = mean of the standard deviations of NN intervals in all 5-minute segments of the entire recording, HF = high frequency power, HRV = heart rate variability, LF = low frequency power, LSD = least significant difference, MD = mean difference, pNN50 = percentage of normal-to-normal intervals differing by more than 50 milliseconds, rMSSD = the square root of the mean of the squares of the differences between adjacent normal-to-normal RR intervals, SDANN = standard deviation of the consecutive 5-min averages of NN intervals, SDNN = standard deviations of all NN intervals.
*$P < .05$ for vs 25(OH)D ≥ 50.

Table 3

Associations of serum 25(OH)D with HRV parameters.

	β value	SE	Standard β value	*t* value	*P* value
Intercept	52.99	15.53	0.00	3.41	<.001
SDNN	0.44	0.35	0.76	1.23	.219
ASDNN	0.05	0.17	0.04	0.27	.791
pNN50	0.76	0.74	0.35	1.03	.306
LF	0.74	0.72	0.31	1.02	.308
HF	−2.87	1.32	−0.87	−2.18	.031
LF/HF	−13.19	7.12	−0.33	−1.85	.066
SDANN	−0.36	0.33	−0.59	−1.09	.276
rMSSD	0.24	0.57	0.17	0.42	.674

ASDNN = mean of the standard deviations of NN intervals in all 5-minute segments of the entire recording, HF = high frequency power, HRV = heart rate variability, LF = low frequency power, pNN50 = percentage of normal-to-normal intervals differing by more than 50 milliseconds, rMSSD = the square root of the mean of the squares of the differences between adjacent normal-to-normal RR intervals, SDANN = standard deviation of the consecutive 5-min averages of NN intervals, SDNN = standard deviations of all NN intervals.

linear regression analysis found the level of 25(OH)D was associated with rMSSD ($P = .002$; Table 4).

4. Discussion

Currently, the prevalence of deficiency or insufficiency of vitamin D is increasing significantly worldwide, and it is estimated that nearly 1 billion people meet the diagnoses for deficiency or insufficiency of vitamin D.[16] Approximately 50% of hypovitaminosis in children and adults occurred in the United States, Canada, Mexico, Europe, Asia, New Zealand, and Australia.[16] Moreover, a previous study found that the frequency of vitamin D deficiency in overweight and obese adults was 93.2%.[17] Lu et al[18] reported the rate of low vitamin D levels among middle-aged

Table 4

Associations of serum 25(OH)D with HRV parameters (variable selection).

	β value	SE	Standard β value	t value	P value
Intercept	32.34	2.80	0.00	11.54	<.001
rMSSD	0.32	0.10	0.22	3.13	.002

Stepwise variables selection: *P* for inclusion is .05, *P* for exclusion is .10.

HRV = heart rate variability, rMSSD = the square root of the mean of the squares of the differences between adjacent normal-to-normal RR intervals.

and elderly individuals in China was 93.6%. Furthermore, studies have found that vitamin D deficiency was more common in diabetic patients.[19–21] This study found that the mean vitamin D levels were 40.30 nmol/L, and the proportions of the deficiency and insufficiency were 28.80% and 46.60%, respectively. This result is similar with the results of a previous study by Jung et al,[22] which found the mean vitamin D level in T2DM patients was 37.75 nmol/L, and the combination of deficiency and insufficiency of vitamin D was 80.4%. However, there are few studies that have addressed the association between vitamin D levels and HRV parameters in T2DM patients. This cross-sectional study recruited 191 T2DM patients and found that SDNN, ASDNN, pNN50, LF, HF, SDANN, and rMSSD were lower in patients with 25(OH)D deficiency. Meanwhile, the 25(OH)D levels of T2DM patients in the deficiency group were associated with higher LF/HF. Moreover, patients' 25(OH)D levels in the insufficiency group were associated with reduced pNN50 and rMSSD. At the same time, we noted insufficiency group was associated with elevated LF/HF, while no significant difference was noted between the insufficiency group and the sufficiency group for SDNN, ASDNN, LF, HF, and SDANN. Finally, the levels of 25(OH)D were positively associated with rMSSD.

A previous study has illustrated that the VDR and the ligand-generating 25-hydroxyvitamin D3 1-α-hydroxylase were observed in the cardiac myocytes, cardiac fibroblasts, vascular smooth muscle cells, and vascular endothelial cells, which play an essential role in cardiovascular health.[23] Moreover, a low vitamin D level was associated with a high risk of hypertension, cardiovascular disease, cardiac death, and all-cause mortality.[24] Mann et al[15] reported a significant association between serum 25(OH)D deficiency and suppression of resting cardiac autonomic activity. A cross-sectional study conducted by Tak et al[25] reported that the 25(OH)D deficient group had a lower SDNN value than the non-deficient 25(OH)D group (25.3 ± 8.4 m/s vs 30.2 ± 16.2 m/s; $P = .044$, respectively). Additionally, SDNN was positively correlated with 25(OH)D levels after adjusting age, sex, and season of 25(OH)D measurement. These results suggested that a low vitamin D level was associated with reduced cardiac autonomic activity.

It is noteworthy that vitamin D deficiency is widely detected in T2DM patients and is associated with several complications.[26,27] CAN was a commonly overlooked diabetic complication, which could affect the cardiovascular, gastrointestinal, and genitourinary systems. The involvement of the cardiovascular system ranged from arrhythmias to sudden death.[28] Moreover, the autonomic imbalance characteristic of the hyperactive sympathetic system and the hypoactive parasympathetic system was significantly correlated with cardiovascular disease in diabetic patients.[29] Studies have already demonstrated the reduced HRV could be regarded as early indicators of cardiac autonomic dysfunction.[7,30,31]

This study found that vitamin D levels of T2DM patients in the deficiency group were associated with reduced SDNN, ASDNN, pNN50, LF, HF, SDANN, and rMSSD. Meanwhile, the LF/HF in the deficiency group was significantly higher than those in the sufficiency group. Moreover, patients in the insufficiency group had lower pNN50 and rMSSD compared to the sufficiency group. Furthermore, the 25(OH)D levels were positively correlated with rMSSD. This result is inconsistent with a previous study by Jung et al,[22] which reported that the SDNN in the supine position was significantly decreased in patients with vitamin D deficiency and 25(OH)D was positively correlated to SDNN. A study by Maser et al,[32] that assessed cardiovascular autonomic function by mean circular resultant and expiration/inspiration (E/I) ratio in patients with T2DM, reported that 25(OH)D insufficiency was associated with reduced parasympathetic function. However, Hansen et al[33] reported a U-shape association between serum vitamin D levels and HRV parameters. The result points out that both high and low vitamin D levels could cause CAN in diabetic patients. A potential reason for this could be that high 25(OH)D levels could motivate 24-hydroxylase to rapidly degrade 1,25(OH) 2 D and 25(OH) D to their 24-hydroxylated inactive forms, which results in the same pathological pathways as low levels of vitamin D.[34,35] Moreover, Canpolat et al[36] reported that vitamin D deficiency could impair cardiac autonomic function, despite the absence of overt cardiac involvement and symptoms. However, Nalbant et al[14] reported no significant association between low vitamin D levels with HRV parameters in subjects with low cardiovascular risk. The potential reasons for this could be as follows: the mean age of patients in the previous study was younger than this study, and the subjects in the previous study had a low cardiovascular risk; and the degree of difference among groups in the previous study was more significant than this study.

The mechanism by which vitamin D exerts its cardio and vasculoprotective effects is functioning by regulating the renin-angiotensin system, glycemic control, inflammatory cytokines, the levels of PTH, calcium deposition in the vascular smooth muscle, and direct vascular actions.[37] Moreover, hyperglycemia can activate several different biochemical pathways related to the metabolic and/or redox state of the cell, and thus can impair the nerve perfusion and contribute to the development and progression of diabetic neuropathies.[38] The earliest manifestations of autonomic neuropathy in diabetes that are correlated with the parasympathetic denervation owing to neuropathy are seen first in the longest fibers.[38] Moreover, CAN is able to change cardiac rhythm, owing to the initial changes in the parasympathetic, followed by the sympathetic modulation of the cardiac rhythm.[39] Furthermore, deficiency of vitamin D could affect insulin synthesis and secretion through changes in calcium levels.[40] Therefore, sufficiency of vitamin D or calcium could regulate the balance between the extracellular and intracellular beta-cell calcium pools.[41]

This study had several limitations. First, the study design as cross-sectional and the causality relationship could not be obtained. Second, a small number of included patients restricted us from conducting more detailed stratified analyses. Third, the severity of T2DM might have affected the HRV parameters, which was not fully illustrated. Fourth, the imbalance of individuals' characteristics among deficiency, insufficiency, and sufficient groups, which might bias the association between serum vitamin D levels and HRV in patients with T2DM. Fifth, the insulin level could be interactive with the effect of vitamin D, while these information was not available. Sixth, the underlying diseases and lifestyle among groups were not available, which might play an important role on HRV parameters. Finally, although the analysis contained both time domain and

frequency domain variables, the causality between vitamin D levels and HRV parameters for T2DM patients could not be obtained, owing to the electronic medical record system-based analysis.

5. Conclusion

This study found that deficiency or insufficiency of vitamin D in T2DM patients is associated with reduced HRV parameters. Hypovitaminosis D was associated with lower HRV parameters, which might induce CAN and further cardiovascular disease risk in patients with T2DM. Furthermore, a large-scale prospective study should be conducted to assess the role of vitamin D on the progression of cardiac autonomic function in patients with T2DM.

Author contributions

Formal analysis: Li Ye Chen, Jin Luo Cheng, Yun Xue.
Resources: Yun Xue, Jie Shao, De Li.
Software: Li Ye Che, Yun Xue, Jie Shao.

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