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Featured Article

Galectin-3 and incident cognitive impairment in REGARDS, a cohort of blacks and whites

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Abstract

Introduction: The relationship between serum galectin-3 and incident cognitive impairment was analyzed in the Reasons for Geographic and Racial Differences in Stroke study.

Methods: Baseline galectin-3 was measured in 455 cases of incident cognitive impairment and 546 controls. Galectin-3 was divided into quartiles based on the weighted distribution in the control group, and the first quartile was the referent.

Results: There was an increasing odds of cognitive impairment across quartiles of galectin-3 (odds ratios, 1.00 [0.68–1.46], 1.45 [1.01–2.10], and 1.58 [1.10–2.27] relative to the quartile 1; *P* trend = .003) in an unadjusted model, which persisted after adjusting for age, sex, and race (*P* = .004). Adjustment for cardiovascular risk factors greatly attenuated this association (odds ratios, 0.97 [0.60–1.57], 1.52 [0.94–2.46], and 1.27 [0.76–2.12]; *P* = .15). The association differed by diabetes status (*P* interaction, .007). Among nondiabetics (293 cases, 411 controls), those with galectin-3 in the fourth compared with first quartile had an odds ratio of 1.6 (0.95–2.99; *P* trend, .02). In diabetics, the odds ratio was 0.23 (0.04–1.33).

Discussion: Serum galectin-3 was associated with increased risk of incident cognitive impairment in a large cohort study of blacks and whites but only in nondiabetics.

Keywords: Galectin-3; Cognitive impairment; Biomarkers; Epidemiology; Incidence; Risk factors

1. Background

Cognitive impairment has risen in importance as a public health issue with approximately eight million adults over the age of 71 years in the United States having some form of cognitive impairment [1]. Every year, nearly 12% of patients with milder levels of cognitive impairment progress to dementia [1]. The increasing cost of care for patients with dementia, and the recent increase in trials aimed at controlling the decline of cognitive function in mildly affected individuals, suggests that early detection of those at risk of developing cognitive impairment is of critical importance [2].

Although various factors may contribute to cognitive decline, it is well established that cardiovascular risk factors play a role [3]. In recent years, the carbohydrate-binding

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lectin galectin-3 has received significant attention in the cardiology arena as a circulating biomarker for cardiovascular risk. Galectin-3 can be nuclear or cytoplasmic in location and has been found to have very diverse influences on cellular functioning [4]. Galectin-3 concentration is independently associated with mortality in the general population and in patients with heart failure [5].

Efforts are now underway to investigate the significance of galectin-3 in relation to diseases of the nervous system. Much of the attention has been focused on cerebrovascular diseases [6], but one study found that patients with Alzheimer's disease had higher serum galectin-3 levels than normal controls [7]. Experimental evidence has shown that galectin-3 is involved in inflammatory responses, myelination, and poststroke angiogenesis [8,9].

Given the close relationship between cardiovascular risk factors and cognitive decline [10] and the burgeoning evidence for involvement of galectin-3 in the functioning of the cardiovascular and nervous systems, we hypothesized that galectin-3 was associated with risk of cognitive impairment. We tested our hypothesis by analyzing the relationship between serum galectin-3 levels and incident cognitive impairment in participants in the Reasons for Geographic and Racial Differences in Stroke (REGARDS) cohort.

2. Methods

The REGARDS study is a population-based cohort, investigating racial and geographical disparities in stroke and cognitive disorders [11]. The cohort consists of 30,239 black and white individuals aged 45 years or older who were enrolled between 2003 and 2007, as described previously [11]. The study sampled blacks and residents of the stroke belt (North Carolina, South Carolina, Georgia, Alabama, Mississippi, Tennessee, Arkansas, and Louisiana). A computer-assisted telephone interview was used to obtain demographic and socioeconomic information, medical history, and verbal informed consent. At a subsequent in-home visit, we obtained written informed consent, physical examination results, blood samples, electrocardiogram (ECG), and medications inventory [11]. The study's methods were reviewed and approved by the institutional review boards at each of the study institutions.

2.1. Measurements and definitions

The Six-Item Screener (SIS; three temporal orientation items, and delayed recall of three objects) was used to determine baseline cognitive status. This measure was validated in community and clinical samples including large numbers of black participants [12]. Scores can range between 0 and 6, with four or fewer indicating cognitive impairment. Hypertension was defined as systolic blood pressure $\geq$ 140 mm Hg, diastolic blood pressure $\geq$ 90 mm Hg, or self-reported hypertension with the use of antihypertensive medications. Diabetes was defined as self-reported use of glucose control medications, fasting glucose greater than 126 mg/dL, or nonfasting blood glucose $>$ 200 mg/dL. Dyslipidemia was defined as total cholesterol $>$ 240 mg/dL, low density lipoprotein cholesterol $\geq$ 160 mg/dL, high density lipoprotein $<$ 40 mg/dL, or on medications to treat dyslipidemia. Smoking status was ascertained by asking participants during the telephone interview if they were current cigarette smokers. Alcohol use was determined through participants' self-report. Furthermore, the National Institute on Alcohol Abuse and Alcoholism classification (none, moderate [0–7/week, women; 0–14/week, men], heavy [7+/week, women; 14+/week, men]) was used to distinguish moderate and heavy drinking. Physical activity was assessed by asking about how frequently the participants engaged in intense physical activity per week (1–3 times/week or four or more times/week). We calculated the estimated glomerular filtration rate using the Chronic Kidney Disease Epidemiology Collaboration formula, with chronic kidney disease defined as estimated glomerular filtration rate $<$ 60 mL/min/1.73 m^2 [13]. Left ventricular hypertrophy was classified using a centrally read ECG. Congestive heart failure was defined based on self-report on orthopnea or paroxysmal nocturnal dyspnea. We used self-report or presence on ECG to determine atrial fibrillation. Prebaseline heart disease was defined by self-reported bypass, myocardial infarction, angioplasty or stenting, or evidence of myocardial infarction on ECG. Prebaseline stroke was defined by self-report of a diagnosis by a physician. Medical records of suspected stroke after baseline were centrally adjudicated as described previously [14].

2.2. Longitudinal cognitive assessment

Participants are contacted every six months to ascertain potential stroke events and cognitive function. Starting in 2006, a three-test battery was performed every 2 years. This included Word List Learning (WLL) and Word List Recall and Semantic fluency (animals), all from the Consortium to Establish a Registry for Alzheimer's Disease [15]. The Word List Learning score is the number of words recalled on a 10-item, three-trial word list learning task (range could be from 0 to 30). The Word List Recall score is the number of words recalled after a filled delay (range could be from 0 to 10). Semantic fluency is the number of animals that could be named in 60 seconds. These tests were administered in a staggered fashion for ease of administration by telephone. We supervised all testing with quality control monitoring.

2.3. Case-control study design

We used a nested case-control study to select a subset of REGARDS participants for galectin-3 measurements and to provide results that would approximate measurement of galectin-3 in the entire cohort. Methods have been reported elsewhere [16]. We excluded participants with prevalent stroke (n = 1930), cognitive impairment at the baseline

SIS administration (n = 2319), missing data (n = 546), stroke before the first SIS (n = 28), or insufficient follow-up cognitive testing at the time of sample selection (n = 7786) and then identified cases from the remaining 17,630 participants. To define incident cognitive impairment, an absolute score approach was used, incorporating adjustment based on regression for age, education, race, and sex on the 3-test cognitive battery [17]. Incident cognitive impairment was defined as scores less than sixth percentile of each participant's age-, race-, and sex-predicted score on two of three components of the most recently administered three-test battery (the components of which have been described above). The most recent score on the three-test battery was used to score cognitive function. A significant fraction of the cohort could not have follow-up cognitive testing done and therefore had to be excluded. We did not follow up changes in cognitive function over time—incident cognitive impairment was defined against a baseline of normal cognitive function.

We selected controls from a cohort random sample of 1100 participants, who had been selected from the entire REGARDS cohort for a case-cohort study on stroke [18]. We used age-, sex-, and race-stratified random sampling (50% black; 50% white; 50% women; 50% men; age groups: 45–54 [20%], 55–64 [20%], 65–74 [25%], 75–84 [25%], and ≥85 [10%]). We then excluded controls using the same criteria for cases, those with insufficient cognitive testing to determine case status, and those who became a case, leaving 587 participants in the control group [16].

2.4. Galectin-3 measurement

During the baseline home visit, fasting blood samples were drawn, processed, and shipped to the University of Vermont for storage [19]. Galectin-3 was measured in the case-cohort sample using an ultrasensitive ELISA (Quantikine ELISA Kit, catalog # DGAL30; R&D Systems, Minneapolis, MN). The ELISA was based on E. coli–expressed recombinant human galectin-3 and antibodies raised against the recombinant protein. We used a Biotek EL808 ELISA reader, and all samples were run in duplicate. The analytical coefficient of variation range was 6%–7%. Galectin-3 was not available in 40 cases and 41 controls due to missing blood samples or technical issues, thus leaving 455 cases and 546 controls for analysis.

2.5. Apolipoprotein E genotyping

We determined apolipoprotein E (*APOE*) genotype status by performing TaqMan genotyping of rs429358 and rs7412 (Applied Biosystems/Thermo Fisher catalog #C_904973_10 and C_3084793_20). For rs429358 (C/T single-nucleotide polymorphism), we used the following primer set: GCT GGGCGCGGACATGGAGGACGTG**c**GCGGCCGCCTGG TGCAGTACCGCGG and GCTGGGCGCGGACATGGAG GACGTG**t**GCGGCCGCCTGGTGCAGTACCGCGG.

For rs7412 (C/T single-nucleotide polymorphism), we used the following primer set: CCGCGATGCCGATGA CCTGCAGAAG**c**GCCTGGCAGTGTACCAGGCCGGGG C and CCGCGAT**G**CCGATGACCTGCAGAAG**t**GCCTGG CAGTGTACCAGGCCGGGGC. The genotyping was performed on an ABI 7900 instrument. Our cycling program was as follows: 50°C for 2 minutes and 95°C for 10 minutes, followed by 40 cycles of 95°C for 15 seconds and 60°C for 1 minute.

2.6. Statistical methods

To account for the stratified selection of the controls, all analyses were weighted up to the original REGARDS cohort distribution. The distribution of baseline characteristics was examined by case or control status. Odds ratios and 95% confidence intervals for the association of galectin-3 with cognitive impairment were calculated using weighted logistic regression. We divided galectin-3 into quartiles based on its weighted distribution in the control group, and the bottom quartile was the reference group. The overall *P* value for galectin-3 quartiles was calculated. A *P* value for the trend in odds ratios across the quartiles was also calculated, using a linear contrast statement for quartiles. The unadjusted model was Model 0. We then used three levels of adjustment to evaluate confounding, based on known correlates of galectin-3 and cognitive function. Model 1 included age, sex, and race. Model 2 added region of residence, education, income, hypertension medication use, smoking status, low density lipoprotein cholesterol, diabetes, systolic blood pressure, left ventricular hypertrophy, alcohol use, physical activity, history of heart disease, atrial fibrillation, and congestive heart failure. Model 3 added the presence or absence of the *APOE* ε4 allele. Furthermore, we looked at which variables had the strongest effect on the relationship between galectin-3 and cognitive decline in Model 2. Because diabetes had the strongest effect, we explored that relationship in detail, including testing for an interaction.

3. Results

The median time from baseline until the most recent three-test battery was 3.4 years among the cases and controls. The correlation of galectin-3 to demographic variables and cardiovascular risk factors has been described in this study [20,21]. The distribution of baseline risk factors among cases and controls in our study is in Table 1. There was no difference in the age, race, and sex distribution between cases and controls. Cases were more likely than controls to live in the southeastern stroke belt; have an annual income <$20,000; and have diabetes, impaired kidney function, a history of heart disease, congestive heart failure, and left ventricular hypertrophy. Cases were more likely to be

Table 1
Baseline characteristics of cases and controls

Baseline risk factor levels, % unless otherwise specified	Cases (N = 455)	Controls (N = 546)*	*P* value†
Black race	33	36	.33
Age, mean	64.5	64.1	.42
Male sex	41	42	.59
Education ≤ high school	34	31	.37
Stroke Belt region	65	53	<.001
Income < $20,000	28	13	<.001
Diabetes mellitus	28	18	<.001
Hypertension	61	56	.10
Dyslipidemia	60	58	.59
Atrial fibrillation	10	9	.69
Left ventricular hypertrophy by ECG	11	7	.02
History of heart disease	20	14	.007
Congestive heart failure	19	13	.007
Current smoker	17	13	.05
Heavy or moderate alcohol use	31	39	.008
No weekly exercise	38	32	.09
BMI (kg/m^2), mean	30	29	.03
Statin use	34	32	.56
eGFR < 60 ml/min/1.73 m^2	14	6	<.001
Apolipoprotein E4 allele present	32	32	.84

Abbreviations: BMI, body mass index; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate.

*Data weighted to analytic cohort, total N = 17,630.

†Pearson chi square (corrected for survey design with the second-order correction of Rao and Scott); Wald F statistic for age and body mass index.

current smokers and have higher body mass index but less likely to be heavy or moderate alcohol users. The *APOE* ε4 allele was similar between cases and controls.

The median galectin-3 level in cases was 10.8 ng/mL (interquartile range, 8.4–13.5), whereas for controls it was 9.9 ng/mL (interquartile range, 7.8–12.8). Table 2 shows the associations of galectin-3 with the risk of developing cognitive impairment. In Model 0, comparing quartile 4 (Q4) to quartile 1 (Q1), the odds of cognitive impairment was increased 58% (odds ratio, 1.58; 95% CI, 1.10–2.27). There was a significant trend across quartiles 1 through 4 (*P* for trend = .003). Adjustment for age, race, and sex in Model 1 did not change the association. In the fully adjusted model, the association was attenuated (odds ratio, 1.27; 95% CI, 0.76–2.12). There was no impact of further adjustment for *APOE* ε4 allele status.

Interaction testing revealed that the relationship between galectin-3 and incident cognitive impairment differed by diabetes status (*P* value for galectin-3–diabetes interaction = 0.007). Comparing cases (n = 293) and controls (n = 411) without diabetes, in a fully adjusted model, increasing galectin-3 levels were associated with increased risk of cognitive impairment (Table 3, *P* for trend = .02). On the contrary, in cases (n = 111) and controls (n = 83) with diabetes, individuals with galectin-3 levels in the fourth quartile had an odds ratio of 0.23 (0.04–1.33) compared with those in the first quartile. However, the trend across the four quartiles was not statistically significant (*P* = .10) (Table 3).

Table 2
Odds ratios of cognitive impairment by baseline galectin-3

	Quartile of galectin-3				
	1	2	3	4	
Model	0.1–7.8 ng/mL	7.8–9.9 ng/mL	9.9–12.8 ng/mL	>12.8 ng/mL	*P* for trend*
Model 0	1 (Ref)	1.00 (0.68–1.46)	1.45 (1.01–2.10)	1.58 (1.10–2.27)	.003
Model 1	1 (Ref)	1.02 (0.69–1.51)	1.49 (1.02–2.17)	1.62 (1.10–2.39)	.004
Model 2	1 (Ref)	0.97 (0.60–1.57)	1.52 (0.94–2.46)	1.27 (0.76–2.12)	.15
Model 3	1 (Ref)	0.98 (0.60–1.59)	1.57 (0.97–2.56)	1.25 (0.75–2.10)	.16

Abbreviations: LDL, low density lipoprotein; Ref, reference group.

NOTE. Model 0: unadjusted.

NOTE. Model 1: adjusted for age, sex, and race.

NOTE. Model 2: adjusted for above + region, education, income, alcohol use, smoking status, physical activity, hypertension medication use, LDL cholesterol, diabetes, systolic blood pressure, left ventricular hypertrophy, history of heart disease, atrial fibrillation, congestive heart failure, and estimated glomerular filtration rate.

NOTE. Model 3: adjusted for above + apolipoprotein e4 allele present.

*Trend across quartiles as an ordinal variable 1, 2, 3, and 4.

Table 3
Odds ratios of cognitive impairment by baseline galectin-3 stratified by diabetes

	Quartile of galectin-3				
	1	2	3	4	
Diabetes status	0.1–7.8 ng/mL	7.8–9.9 ng/mL	9.9–12.8 ng/mL	>12.8 ng/mL	*P* for trend*
No diabetes (293 cases, 411 controls)					
Model 2	1 (Ref)	1.22 (0.73–2.05)	2.30 (1.38–3.84)	1.68 (0.95–2.99)	.02
Diabetes (111 cases, 83 controls)					
Model 2	1 (Ref)	0.30 (0.06–1.61)	0.23 (0.05–1.14)	0.23 (0.04–1.33)	.10

Abbreviations: LDL, low density lipoprotein; Ref, reference group.

NOTE. Model 2: adjusted for age, sex, race, region, education, income, alcohol use, smoking status, physical activity, hypertension medication use, LDL cholesterol, systolic blood pressure, left ventricular hypertrophy, history of heart disease, atrial fibrillation, congestive heart failure, and estimated glomerular filtration rate.

*Trend across quartiles as an ordinal variable 1, 2, 3, and 4.

4. Discussion

In this prospective observational study of black and white men and women older than 45 years, higher galectin-3 concentration was associated with increased odds of incident cognitive impairment. To the best of our knowledge, this is the first large population-based cohort study to report the association between galectin-3 and cognitive impairment. This relationship was found in the unadjusted model and in the model that was adjusted for age, sex, and race but was attenuated after further adjustment for traditional risk factors. Furthermore, in the fully adjusted model, the association between higher galectin-3 levels and cognitive impairment was present only in individuals without diabetes (P interaction = .007).

Many cardiovascular risk factors are associated with cognitive function [3,10]. Some other recent studies have also investigated the relationship between galectin-3 and cognitive function [22,23]. Given the general association of higher galectin-3 levels with worse cardiovascular disease status, we would expect galectin-3 to show a similar positive correlation with cognitive impairment. A cross-sectional study that compared patients with Alzheimer's dementia with healthy controls found that the patients had higher serum galectin-3 levels [7]. However, the difference in galectin-3 levels between the controls and a group with mild cognitive impairment was not significant. In addition, the severity of cognitive impairment, as indicated by the Mini-Mental Status Examination score, was significantly correlated to galectin-3 levels in controls and patients with Alzheimer's dementia, leading the authors to suggest that it might be of value as a biomarker that correlates with worsening of cognition over time. Our findings suggest that this may be the case, but we did not evaluate longitudinal score changes in global cognitive functioning. On the other hand, a study that compared serum proteomics in 35 patients with amnestic mild cognitive impairment and 35 healthy controls [22] found that the former group actually had lower serum levels of galectin-3–binding protein in the serum. This protein binds to galectin-3, but its function has not been investigated in as much detail. Although the mechanisms behind this relationship are not clear, it is possible that lower galectin-3–binding protein levels indicate higher levels of free galectin-3, which may be more biologically active.

The mechanisms behind the putative relationship of galectin-3 to cognitive impairment are not clear at this time. One possibility is that higher galectin-3 levels indicate impaired blood supply to the brain. Carotid atherosclerosis and heart failure, both of which are associated with higher galectin-3 levels [24,25], are also linked to worse cognitive function [26,27]. The second major potential mechanism to consider relates to inflammation. Galectin-3 is not thought to be normally expressed in the brain, with microglia and other cells producing it after a wide variety of brain injuries [28]. Deletion of the galectin-3 gene improves recovery from neurological injury in animal models [29], and it is conceivable that chronically elevated galectin-3 levels in the blood might reflect impairment of the brain's ability to recover from injury such as ischemia. Galectin-3 has also been shown to suppress the release of the interleukin IL-10 [30], which has neuroprotective effects in Alzheimer's disease [31]. Apoptosis, which is believed to be triggered by beta-amyloid in the neurons of patients with Alzheimer's disease [32], has also been shown to be regulated by galectin-3 although the exact mechanisms remain unclear [28]. Altogether, over time, these diverse effects of galectin-3 on the nervous system might accumulate and reveal themselves as the cognitive impairment that we detected using our screening tools. Finally, variant alleles of the rs4644, rs4652, and rs1009977 single-nucleotide polymorphisms of the *LGALS3* gene (that codes for galectin-3) were associated with small but significant impairment in cognitive function compared with the wild-type alleles in elderly persons who were enrolled in the Prospective Study of Pravastatin in the Elderly at Risk cohort [23]. Although the authors did not investigate the relationship of these alleles to galectin-3 concentration, they did find them to be associated with higher levels of C-reactive protein, another inflammatory marker. This suggests that galectin-3 may play a causative role, as opposed to being a marker of other processes that lead to cognitive impairment.

The unexpected finding from our study was that the relationship between galectin-3 and cognitive function held only for those participants who did not have diabetes in a fully adjusted model. In those with diabetes, there was a trend toward less incident cognitive impairment particularly in those with higher galectin-3 levels although it was not statistically significant ($P = .10$). Such an interaction has not been consistently seen in other conditions—for instance, diabetes status does not seem to impact the relationship between galectin-3 levels and heart failure [33], microalbuminuria [34], or stress-induced angina [35].

Galectin-3 levels are higher in persons with diabetes [36], and there is some evidence that it performs some unique functions in persons with diabetes. This might lead to the loss of the relationship with cognitive decline in diabetic individuals. For example, galectin-3 has been found to be important in the scavenging of advanced glycation endproducts that are formed during diabetes [37]. Interestingly, this scavenging function has been noted to have tissue-specific effects [38]. Although galectin-3 deficiency protected against advanced glycation endproduct-induced retinal damage in a model of diabetes [39], it accelerated diabetes-induced glomerular damage in another study [40]. Thus, galectin-3 might perform some tissue-specific functions in the brains of persons with diabetes which disrupt the correlation to cognitive decline that is evident in persons without diabetes. The underlying explanation for these findings likely relates to the highly pluripotent roles that galectin-3 can play and its varying locations in the cellular and extracellular areas.

4.1. Strengths and limitations

Strengths of our study included the prospective case-control study design because this gave us greater efficiency in measuring galectin-3 in only a subset of the cohort. The study design also minimized reverse causality because our exposure is measured before our outcome. Furthermore, our rich data set allowed us to adjust for several confounders. Attrition was also quite low. Our technique for determining cognitive impairment captured clinically relevant levels of dysfunction and has been validated elsewhere [16].

Our study had a relatively small sample size for those with diabetes, and therefore, the odds ratio estimates may not be highly precise. However, the interaction was highly significant, so our conclusion that there was a difference between diabetics and nondiabetics is warranted. Other limitations include the relatively short follow-up time, lack of brain imaging, lack of evaluation for dementia, and measurement of galectin-3 at one timepoint instead of measuring serially over time. Our use of the baseline SIS allowed us to exclude those with significant baseline cognitive impairment, but those with milder levels of impairment were not excluded, which might have biased our results toward the null. We also did not have echocardiography data to determine presence and extent of heart failure, which may have interfered with our ability to adjust for this factor completely. Our study also did not look at the mechanism behind the cognitive impairment noted in our patients, and therefore, we cannot state if the difference was due to pathology similar to that seen in Alzheimer's disease, vascular dementia, or other conditions.

5. Conclusions

In a large prospective longitudinal cohort study of blacks and whites, higher galectin-3 was associated with increased risk of incident cognitive impairment but only in those without diabetes. Although our work adds an important finding to the literature showing relationships of cardiovascular and inflammatory disease markers with brain functioning, future studies should confirm our findings and investigate the mechanisms behind this association. Additional topics that remain to be addressed include the relationship of galectin-3 to various forms of dementia and to rates of progression. It must be investigated if measures to reduce circulating galectin-3 levels can improve cognitive functions. Finally, whether a multibiomarker panel approach would increase the yield for early detection of cognitive impairment remains to be established [41].

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RESEARCH IN CONTEXT

1. Systematic review: The authors reviewed the relevant studies on association of galectin-3 with cognitive impairment and neurological disorders using PubMed and Google scholar by going through the references of the relevant articles which are cited in this article.
2. Interpretation: Our study found increasing odds of cognitive impairment across quartiles of galectin-3 in a model adjusted for demographic variables (age, sex, and race). Adjustment for cardiovascular risk factors attenuated this association. A significant interaction by diabetes status was found in the study population.
3. Future directions: Further studies are needed to confirm our findings and to see if this relationship holds true for every variant of cognitive impairment. A multibiomarker panel that includes galectin-3 could allow for earlier detection of cognitive impairment.

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