

**RESEARCH REPORT**

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Relation of exercise and pain in patients with idiopathic distal axonal polyneuropathies

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Abstract

Although exercise is associated with better outcomes in patients with some peripheral neuropathies, data in idiopathic peripheral neuropathies is lacking. This study was completed to do a comprehensive data analysis about the benefits of regular exercise in a well-characterized cohort of patients with idiopathic distal, symmetrical, axonal polyneuropathy enrolled in the Peripheral Neuropathy Research Registry (PNRR) at Johns Hopkins University School of Medicine. From the patient-reported exercise habits, metabolic equivalents (METs) were calculated and the patient information was grouped into four categories. The PNRR data set, including patient reported pain, numbness, and weakness, was analyzed using the METs categories to evaluate for the benefits of exercise. We controlled for the components of metabolic syndrome including Hemoglobin A1c (HbA1c), systolic and diastolic blood pressure (BP), high density lipids (HDL) and triglyceride level, and body mass index (BMI) as defined by the Adult Treatment Panel III Guidelines. Lower METs were associated with neuropathic pain, but not with other peripheral neuropathy symptoms. Patients with IPN who exercised were less likely to have painful neuropathy independent of the average METs per week ($P < .01$). No significant differences were seen for patient reported numbness, weakness, or balance issues. The data suggests that patients with idiopathic neuropathy benefit from exercises even if performed on a low intensity level or less frequently, and patients are less likely to have severe pain symptoms when exercising on a regular basis.

KEYWORDS

exercise, idiopathic axonal peripheral neuropathy, METs

1 | INTRODUCTION

Distal, symmetrical polyneuropathies (PN) are progressive disorders with a prevalence of about 15% in adults 40 years and older in the

United States.¹ Hyperglycemia is the most common cause of PN and in patients with diabetes, nearly 50% will develop neuropathy at some point in the course of their disease.² But for ~40% of all patients,³ between 5 and 8 million Americans,⁴ no underlying etiology can be identified even after extensive clinical evaluations. The available pharmacologic treatments for idiopathic polyneuropathy (IPN) are limited to symptom management. There are no therapies known to reverse or slow disease progression.⁵ Alternatively, exercise may offer patients with IPN a means to reduce symptoms, promote nerve health, and

Abbreviations: BP, blood pressure; DM2, diabetes mellitus type 2; DPN, diabetic polyneuropathy; HDL, high density lipids; IGT, impaired glucose tolerance; IPN, idiopathic polyneuropathy; METs, metabolic equivalents; NCS, nerve conduction studies; OR, odds ratio; PN, polyneuropathy; PNRR, peripheral neuropathy research registry; RCT, randomized clinical trial; TNSr, total neuropathy score revised.

improve function. Almost all of the previous studies evaluating the benefits of exercise for PN, have been conducted in patients with diabetes mellitus type 2 (DM2), metabolic syndrome, or impaired glucose tolerance (IGT). No research has been done to understand how exercise is related to these outcomes in IPN.

In randomized clinical trials (RCTs) of those with DM2, exercise is associated with improved glycemic control and control of other cardio-metabolic measures,^{6,7} reduced risk of developing PN,⁸ and improved small fiber function.⁹ Moreover, in those with IGT but not DM2, exercise and dietary control were related to improved metabolic measures, a reduced risk of progression to DM2,¹⁰ and improved small fiber function.¹¹ Because metabolic syndrome, dyslipidemia, and obesity play a role in many cases of IPN as well,¹² we considered whether exercise would lead to positive outcomes in IPN.

In RCTs of those with diabetic polyneuropathy (DPN), aerobic and non-aerobic exercises were consistently associated with reduced PN symptoms,¹³ slowed PN progression,¹⁴ decreased levels of pro-inflammatory cytokines,¹⁵ and improved Nerve Conduction Study (NCS) outcomes.^{14,16,17} Tai Chi or Yoga intervention in those with DPN, showed that isometric and anaerobic exercises were directly related to reduced neuropathy symptoms.¹⁸⁻²¹

Previous studies of exercise and IPN have been limited to patients with either IGT or metabolic syndrome. Moreover, intervention studies have been confined to controlled treatment exercise periods and with specific exercise regimens for just 8 to 16 weeks, without long-term follow-up. We used cross-sectional data from the Peripheral Neuropathy Research Registry (PNRR), a large cohort of patients with PN, to determine the relation of self-reported exercise to PN severity in patients with IPN and to specifically determine if the relationship differed from what has been observed in patients with DPN.

2 | MATERIALS AND METHODS

2.1 | Study population

PNRR is a multicenter cohort of well-characterized patients with distal, symmetrical polyneuropathies, sponsored by the Foundation for Peripheral Neuropathy.²² In mid-2016, the PNRR data set was supplemented with a short one-page exercise questionnaire for all patients enrolled at Johns Hopkins University (Supporting Information). The registry enrolls patients with DPN, IPN, chemotherapy-induced polyneuropathy, and HIV-induced polyneuropathy. If the enrolling physician determined hyperglycemia to be the cause of their PN, patients were enrolled as DPN. DM2 was defined in accordance with American Diabetes Association Guidelines²³ as a fasting glucose greater than or equal to 126 mg/dL, a 2-hour oral glucose tolerance test of greater than or equal to 200 mg/dL, or a HbA1c greater than or equal to 6.5%. If patients had neuropathy symptom onset after their diagnosis of DM2, they were enrolled with diagnosis of DPN. IPN was defined as a slowly progressive, symmetric distal axonal polyneuropathy with unknown cause whereby all other causes, such as

amyloidosis, chronic renal failure, alcohol abuse, vitamin deficiencies, or inherited neuropathies were ruled out. Participants with elevated glucose levels must have had symptoms for at least 2 years prior to their diagnosis of DM2 or IGT to be considered with IPN. Only patients with a diagnosis of IPN were included in this data analysis.

All records of IPN patients enrolled in PNRR at Johns Hopkins before April 2020 were reviewed and included in this analysis if the records met the following criteria for: (a) diagnosis of IPN; (b) exercise data available; and (c) complete PNRR data record. Three hundred twenty-four (324) patients met the inclusion criteria. Of 312 otherwise complete records collected prior to the use of the exercise questionnaire, 58 patients had detailed information regarding exercise frequency, duration, and type in their medical record to also meet the inclusion criteria. The remaining 266 participants provided exercise data by completing the supplemental questionnaire. The study was approved by the Johns Hopkins University Institutional Review Board.

2.2 | PNRR data set

The PNRR data set collected from each patient included: (a) a neurological examination that captured muscular strength evaluations, deep tendon reflexes, sensory features, gait evaluations, and Romberg; (b) NCS evaluations of major motor and sensory nerves in both upper and lower extremities; (c) laboratory testing results for the most common etiologies associated with PN and including testing results for the evaluation recommended by the American Academy for Neurology²⁴; and (d) history questionnaire that asked patients to evaluate the nature and severity of their PN symptoms (ie, pain, numbness, weakness, balance, and autonomic symptoms) including the duration, location, frequency, and severity of symptoms. The questionnaire also captured their medication intake as well as patient and family medical history.²² Painful neuropathy was defined by the physician in the neurological exam as well as self-reported by patients on the questionnaire. For analysis we looked at the relation of exercise and both physician and patient-reported pain. The exam results including pinprick sensibility, vibration sensibility, strength, and tendon reflexes along with degree of symptom extension as measured by pain and numbness were analyzed using the Total Neuropathy Score Revised (TNSr)²⁵ (Table S2a-b). We also collected data for the components of metabolic syndrome including Hemoglobin A1c (HbA1c), systolic and diastolic blood pressure (BP), high density lipids (HDL) and triglyceride level, and body mass index (BMI) as defined by the Adult Treatment Panel III Guidelines.²⁶

2.3 | Exercise questionnaire

The exercise questionnaire asked about "...exercise habits in the last six months" and captured frequency, duration and type of exercise performed. Because exercise duration and intensity varied substantially, we derived the comprehensive metabolic equivalents of task (METs)²⁷ (Table S3) for each participant. Exercise frequency, the average of reported work-out duration (if patients reported multiple

durations for multiple exercises or a range of workout duration) and exercise type (or mean METs if patient reported multiple types of exercises) were used (Table S4). Specifically, an average daily METs was approximated as:

$$\text{METs} = \frac{\text{Average METs Across Activities} * \text{Frequency} * \text{Duration}}{\text{Month} * 30}$$

Four levels of METs/day, on average, were defined for analysis as: 0, 1-60, 61-161, and 161+. The most frequent exercise category was no activity (n = 124), whereas the low, medium, and high activity groups were equally divided (n = 67; n = 67; n = 66). The PNRR data set was analyzed using the METs categories to evaluate for the benefits of exercise. We controlled for the components of metabolic syndrome including Hemoglobin A1c (HbA1c), systolic and diastolic blood pressure (BP), high density lipids (HDL), and triglyceride level, and body mass index (BMI) as defined by the Adult Treatment Panel III Guidelines.²⁶

2.4 | Statistical analysis

Differences in baseline characteristics were evaluated by independent t-tests using STATA. Binary logistic regression analysis was used to determine the association between the different METs categories and pain. The first METs category (METs = 0) was defined as reference category. Odds ratios (ORs) were standard adjusted for age, gender, and BMI. Furthermore, in a secondary analysis we adjusted for the remaining components of the

metabolic syndrome (HbA1c, systolic and diastolic BP, HDL, triglycerides). Missing values for HDL and triglycerides were handled with multiple imputation with the Hmisc package version 4.4.0 on the statistical software R version 3.6.2 (<http://www.r-project.org/>), using multiple reiterations (n = 100) of predictive mean matching with optional weighted probability sampling of the other variables. A logistic regression with the four categories as continuous variant was used to check whether there was a linear trend. All final analyses were performed with the statistical software R version 3.6.2 (<http://www.r-project.org/>).

3 | RESULTS

Results are summarized comparing IPN patients with pain and without pain on independent variables including demographic, cardiometabolic, and PN measures followed by analyses of the relation of IPN neuropathy signs and symptoms with exercise, without and with control for potentially confounding factors.

3.1 | IPN with and without pain: Demographics and cardio-metabolic markers

Baseline characteristics of IPN patients with and without pain are presented in Table 1. The two groups differed in age ($P < .001$), sex ($P < .01$), height ($P < .05$), and diastolic BP ($P < .05$).

TABLE 1 Baseline characteristics in non-painful and painful neuropathy

Variables	Neuropathy type		P-value
	Non-painful N = 85 mean ± SD	Painful N = 239 mean ± SD	
Demographics			
Age (years)	66.7 ± 12.5	60.6 ± 13.9	.0004
Male (%)	77.7	58.6	.0016
Height (cm)	177.7 ± 9.9	174.6 ± 10.7	.0189
Weight (kg)	88.4 ± 22.8	88.2 ± 22.4	.9342
BMI (kg/m ²)	27.8 ± 6.0	28.8 ± 6.5	.2105
Cardio-metabolic Markers			
HbA1c (% hemoglobin)	5.9 ± 1.1	5.8 ± 9.3	.2294
% missing	12.9	15.9	
Triglycerides (mL/dL)	133.7 ± 64.2	141.3 ± 1.1	.5862
% missing	35.3	40.2	
Cholesterol (mL/dL)	183.0 ± 54.8	183.2 ± 39.9	.9707
% missing	36.5	40.2	
LDL (mL/dL)	105.6 ± 45.8	105.6 ± 42.5	.9976
% missing	37.6	41.4	
HDL (mL/dL)	50.4 ± 17.1	54.0 ± 18.7	.2697
% missing	37.6	40.6	
Systolic BP (mmHg)	129.5 ± 17.3	127.7 ± 17.3	.3973
Diastolic BP (mmHg)	73.3 ± 9.3	76.4 ± 10.0	.0144
Time with PN (years)	5.8 ± 6.0	5.5 ± 5.3	.6385

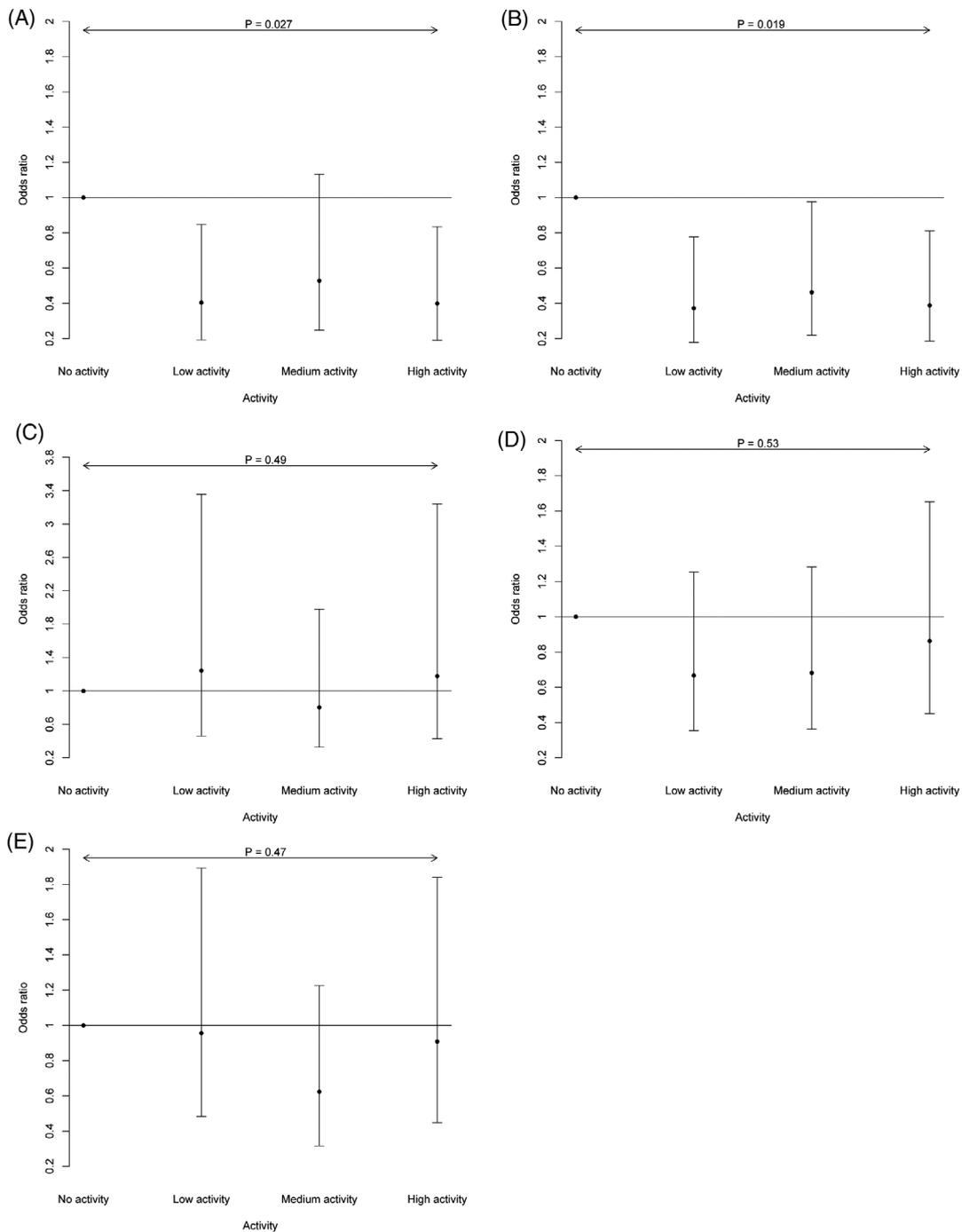


FIGURE 1 METs categories in IPN correlated with risk of painful neuropathy, A, and patient-reported pain, B, but not with numbness, C, weakness, D, or balance E

3.2 | Relation of PN and METs category

Few significant relations were observed between exercise measures and clinical exam evaluation outcomes, and in contrast, a number of significant associations were observed for relations among exercise and self-reported symptom measures.

Patients with IPN who exercised were less likely to have painful neuropathy independent of the average METs per week ($P < .01$). For the low and high activity group, exercise is significantly associated

with a lower risk of painful neuropathy and in the medium activity group the effect did not reach significance. There appears to be no decline of ORs for painful neuropathy with increasing exercise level (Figure 1A). A similar relation was seen for IPN patients who self-reported pain on the questionnaire ($P < .05$) (Figure 1B). No significant differences were seen for patient reported numbness, weakness, or balance issues (Figure 1C-E).

Because both IPN and exercise have been related to metabolic syndrome in the past, we repeated the logistic regression with

additional adjustment for the remaining components of metabolic syndrome (HbA1c, systolic BP, diastolic BP, HDL, and triglycerides). This did not alter our findings, as the risk of painful neuropathy still decreased with exercise ($P < .05$) (Figure 2).

We initially did analysis with both exercise frequency and METs but saw a nearly identical relation, so for the results we only report the effect of METs on outcome variables. Most other outcomes were not significantly related to METs category including TNSr score and NCS outcomes (Table 2).

4 | DISCUSSION

While previous research has examined the relation of exercise and PN measures in patients with DPN, relatively little is known about the effects of exercise in those with IPN. In this study, we examined and

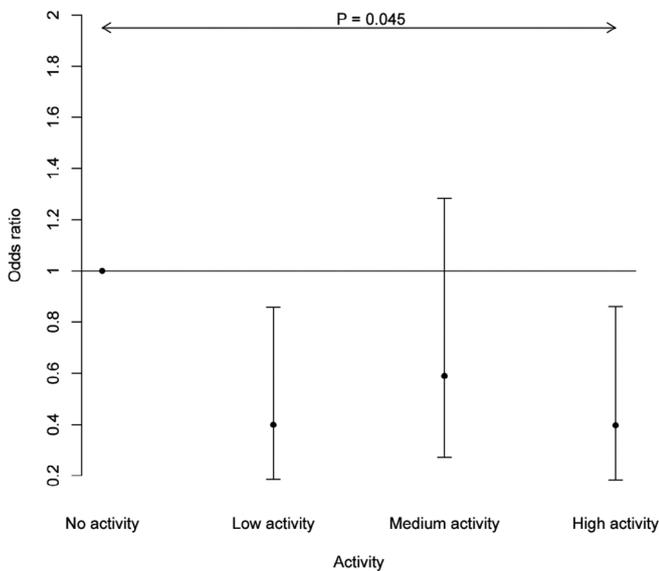


FIGURE 2 METs categories correlated with patient reported pain after controlled for metabolic syndrome factors

compared the relations of exercise and PN measures among IPN patients across METs, a comprehensive measure of energy expenditure. Our results are consistent with results seen in DPN in terms of self-reported outcomes but did not show similar results to better outcomes in NCS or sensory exam.

In our sample, exercising is associated with lower risk of painful neuropathy and patient-reported pain in those with IPN. Most prior studies on the effects of exercise on neuropathy have focused on those with DPN in relatively small randomized controlled studies where the exercise regimen was prescribed (eg, three sessions per week). Our study is consistent with some prior studies in those with DPN, which showed that a 10-week exercise routine significantly decreased worst pain measures.¹³ Our questionnaire asked about average pain in the last 7 days and the results suggest that independent of metabolic syndrome covariates, those with IPN who exercise are less likely to have painful neuropathy.

In IPN, there was no dose-dependent response of higher exercise level. This suggests that independent of exercise duration or intensity, exercise leads to beneficial effects for painful neuropathy. Metabolic syndrome components, particularly abdominal obesity and hypertension are often contributing factors to symptoms experienced in IPN,²⁸ but in our study, even when controlled for metabolic syndrome components, exercise still showed a positive effect for painful neuropathy. This novel finding is important as prior research on the effects of exercise has focused on patients with diabetes and shown a decreased chance of PN⁸ and improved small fiber function⁹ or on those with metabolic syndrome.¹⁵ Although some idiopathic neuropathies may be caused by elevated levels of reactive oxygen species resulting from components of metabolic syndrome or other causes may play a role in neuropathy²⁹ this may not be the case for all IPN patients. Regardless, it is possible that exercise helps to slow the progression of IPN, as measured by pain, as is seen in DPN.¹⁴

Further, our study offers a unique perspective on exercise and neuropathy as we examined clinical outcomes in IPN patients across a diverse range of exercise frequencies and types and relied on self-defined exercise routines which likely corresponds to what people actually do rather than regimented protocols in RCTs. One major

TABLE 2 Risk of painful neuropathy and patient-reported outcomes by METs Category

Outcome measure	Exercise frequency				P trend
	No exercise (N = 124)	Low Activity (N = 67)	Medium Activity (N = 67)	High Activity (N = 66)	
Painful neuropathy ^a	1.0	0.40 (0.19-0.85)*	0.59 (0.24-1.13)	0.40 (0.19-0.83)*	.027
Self-reported pain ^a	1.0	0.37 (0.18-0.78)**	0.46 (0.22-0.98)*	0.39 (0.19-0.81)*	.019
Self-reported numbness ^a	1.0	1.24 (0.46-3.36)	0.80 (0.33-1.98)	1.18 (0.43-0.75)	.49
Self-reported weakness ^a	1.0	0.67 (0.35-1.25)	0.68 (0.36-1.28)	0.86 (0.45-1.65)	.53
Self-reported balance difficulty ^a	1.0	0.91 (0.45-1.84)	0.62 (0.31-1.23)	0.91 (0.45-1.84)	.47
Painful neuropathy ^b	1.0	0.40 (0.19-0.86)*	0.59 (0.27-1.3)	0.40 (0.18-0.86)*	.045

^aLogistic regression adjusted for age, gender, BMI.

^bLogistic regression adjusted for age, gender, BMI, HbA1c, systolic and diastolic blood pressure, HDL, and triglyceride.

** $P < .05$; *** $P < .01$; **** $P < .001$.

limitation in this study is that exercise questions asked participants to consider their habits for the last 6 months. In addition, because we do not have data on patient exercise habits before and after their pain began, we cannot conclude whether exercise *decreases* neuropathy symptoms, or that those with more advanced symptoms exercise in order to prevent further progression. Another limitation of this study is that it does not take into account the reasons that patients do not exercise. Patients with painful neuropathy may naturally be less inclined to exercise as it increases temporary pain making it hard to consider the long-term benefit of the exercise. The association of exercise with a decreased chance of having painful neuropathy could be influenced, in part, by the selective discontinuation of exercise among those with high pain or reverse causation. Therefore, in the future it would be useful to capture the reasons patients do not exercise (ie, pain, lack of time, lack of access to facilities) and to capture exercise habits before and after painful neuropathy begins. Furthermore, our study does not clarify the mechanisms by which exercise decreases the chance of painful neuropathy given the cross-sectional study design and lack of temporality in terms of habits before and after pain. Further research needs to dissect the effect of exercise on both mental and physical outcomes as perceived pain may decrease due to neuropsychological changes. Perceived control may also play a role in the decision patients make to exercise, whereas emotions may play a smaller role in mediating engagement in physical activity³⁰ and controlled clinical trials for patients with IPN would help answer these questions.

Pain is prevalent in IPN and significantly impacts patient quality of life,³¹ so the possibility of exercise as a remedy for pain is promising, as long as pain levels remain tolerable during exercise. In the future, randomized clinical trials should be done with IPN patients to further explore the effect that exercise has on subjective pain and numbness as well as other outcomes such as NCS and objective measures. Our study provides evidence that exercise in those with IPN has a positive effect on reported pain but does not impact other self-reported measures like numbness or weakness. These results suggest that exercise should be considered a treatment option for patients with IPN, particularly those with painful neuropathy.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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