High Prevalence of Hypovitaminosis D Status in Patients With Early Parkinson Disease

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Background: Vitamin D insufficiency has been reported to be more common in patients with Parkinson disease (PD) than in healthy control subjects, but it is not clear whether having a chronic disease causing reduced mobility contributes to this relatively high prevalence.

Objective: To examine the prevalence of vitamin D insufficiency in a cohort of untreated patients with early PD (diagnosed within 5 years of study entry).

Design, Setting, and Patients: The Deprenyl and Tocopherol Antioxidative Therapy of Parkinsonism (DATATOP) cohort is a well-characterized cohort of subjects with early, nondisabling PD. The cohort is well suited for examining the prevalence of vitamin D insufficiency early in the course of the disease. We conducted a survey study of vitamin D status in stored blood samples from patients with PD enrolled in the placebo group of the DATATOP trial. Samples from baseline visits and end point/final visits (mean [SD], 18.9 [13.1] months) were analyzed for 25-hydroxyvitamin D (25[OH]D) concentration in blinded fashion.

Main Outcome Measures: The mean vitamin D concentration and the prevalence of vitamin D insufficiency at baseline and end point/final visits.

Results: Among 199 subjects, 170 (85.4%) had samples from the baseline and end point visits available for analysis; 13 were excluded (10 with low probability of having PD and 3 with 25[OH]D concentrations >3 SDs above the mean). In the remaining 157 subjects, the mean (SD) 25(OH)D concentrations at the baseline and end point visits were 26.3 (8.6) ng/mL and 31.3 (9.0) ng/mL, respectively (to convert to nanomoles per liter, multiply by 2.496). The prevalence of vitamin D insufficiency (25[OH]D concentration <30.0 ng/mL) was 69.4% at baseline and 51.6% at the end point.

Conclusions: The prevalence of vitamin D insufficiency in patients with early PD was similar to or higher than those reported in previous studies. Vitamin D concentrations did not decline during progression of PD. Further studies are needed to elucidate the natural history and significance of vitamin D insufficiency in PD.

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VITAMIN D IS NO LONGER considered a vitamin but rather a hormone with autocrine and paracrine functions well beyond those of regulating calcium homeostasis and bone health. Vitamin D regulates the gamut of physiological processes that go awry in disease states, including cell proliferation, differentiation, and survival as well as resistance to oxidative stress, regulation of other hormones, and immune modulation.[1] Vitamin D insufficiency has been associated with a variety of clinical disorders and chronic diseases,[1] including impaired balance, decreased muscle strength, mood and cognitive dysfunction, autoimmune disorders such as multiple sclerosis and diabetes (types 1 and 2), and certain forms of cancer.[1-6] Furthermore, it has recently been proposed that low vitamin D levels may play a role in the pathogenesis or progression of Parkinson disease (PD).[7,8]

Vitamin D receptors are widespread in the body, including muscle, spinal cord, and brain, supporting the notion that vitamin D is necessary for normal functioning of the peripheral and central nervous systems.[7,9] Both 1α-hydroxylase, the enzyme responsible for activating vitamin D, and the vitamin D receptor are widely distributed in areas of the brain known to be affected in PD and other disorders of gait and balance.[8,9] Also, the vitamin D response element, through which vitamin D modulates gene expression, has been found in more than 900 genes.[10] In fact, vitamin D is involved in regulation of tyrosine hydroxylase gene expression, which can regulate dopamine biosynthesis,[11] and in the expression of brain-derived neurotrophic factor and glutathione, both of which are implicated in the pathogenesis of PD.

However, what constitutes an optimal blood concentration of 25-hydroxyvitamin D (25[OH]D) (the major circulating and storage form of vitamin D) in the hu-

man nervous system remains unknown. Ultraviolet B radiation to the skin converts 7-dehydrocholesterol to provitamin D_3, which is rapidly converted to vitamin D_3 and then in the liver to $25(OH)D_3$. Because it has a relatively long half-life of 2 to 3 weeks, $25(OH)D$ is the best indicator of vitamin D status. Plasma or serum $25(OH)D$ concentration reflects an individual's vitamin D status during the previous 1 to 2 months, similar to how the glycosylated hemoglobin level reflects glucose control. Major determinants of $25(OH)D$ concentration include latitude, season, age, skin tone, and body mass index (BMI; calculated as weight in kilograms divided by height in meters squared). Dietary and multivitamin (MVI) or calcium/vitamin D supplement intakes typically provide less than 400 IU of daily intake and provide a relatively small contribution to circulating levels of $25(OH)D$.[12-15] Recently published literature suggests that the $25(OH)D$ concentration should be greater than 30.0 ng/mL (to convert to nanomoles per liter, multiply by 2.496) for the vitamin D level to be considered sufficient for skeletal health.[9] Vitamin D may offer neuroprotection via multiple mechanisms, with a U-shaped dose-response curve and loss of neuroprotection or even detriment at high, presumably supraphysiological dosages.[16-18] Thus, it will be important to elucidate what constitutes an optimal vitamin D concentration for nonskeletal physiology.

High prevalence of hypovitaminosis D has been reported in PD.[19,20] We found a significant decrease in vitamin D levels in patients with PD compared with matched healthy control subjects and patients with Alzheimer disease,[20] but we did not find a correlation with duration of disease symptoms. Other previous reports also noted high prevalence of vitamin D deficiency in PD,[19] but in contrast, the prevalence was higher in patients with later-stage PD than in those with early-stage PD, consistent with the possibility that having PD and reduced mobility contributes to this relatively high prevalence. The Deprenyl and Tocopherol Antioxidative Therapy of Parkinsonism (DATATOP) cohort is a well-characterized cohort of subjects with early PD.[21] The cohort is well suited for further examining the prevalence of vitamin D insufficiency early in the course of the disease. Subjects in this cohort also experienced clinically significant disease progression, allowing a preliminary examination of whether vitamin D concentration changes as the disease worsens clinically. We report vitamin D status in patients with early PD and examine changes in $25(OH)D$ concentration from baseline to the DATATOP study-defined end point or final visit.

<div style="text-align:center">**METHODS**</div>

STUDY SUBJECTS

The study sample was drawn from 199 subjects randomized to the placebo arm of the DATATOP study. Briefly, DATATOP was a multicenter, randomized, double-blind, placebo-controlled trial with a 2 × 2 factorial design investigating whether selegiline hydrochloride or high-dose vitamin E supplementation slowed disease progression in patients with early PD.[21] The primary end point in the DATATOP study was the development of sufficient clinical disability to warrant initiation of le-

vodopa therapy. The study was conducted at 28 sites in the United States and Canada; enrollment began September 3, 1987, and ended November 15, 1988. Pertinent eligibility criteria were age between 30 and 70 years and a diagnosis of idiopathic PD within the previous 5 years with mild symptoms not yet requiring medical therapy. Pertinent exclusion criteria included intake of vitamin supplements whose contents exceeded amounts found in a One A Day MVI supplement (Bayer Healthcare LLC, Morristown, New Jersey) within the month prior to study enrollment, Mini-Mental State Examination score lower than 22, and Hamilton Scale for Depression score higher than 16. The exclusion of participants taking high-dose vitamin supplements ensured that subjects had not been taking a supplement containing more than 400 IU of vitamin D. Patients enrolled in the DATATOP study were offered the choice of taking a study-supplied MVI supplement that contained 400 IU of vitamin D.

Subjects were initially enrolled into the DATATOP study with a presumptive diagnosis of idiopathic PD, and investigators rated their confidence that PD was the most likely diagnosis at multiple visits or retrospectively for subjects who ceased participation in DATATOP before this item was collected.[22] In addition, great effort was undertaken to determine the likelihood of PD by alternative methods, including record reviews, autopsies, and telephone calls to the sites to clear up any inconsistencies in the case report forms. Owing to the availability of follow-up information for the subjects in the DATATOP cohort, we were able to exclude subjects from this analysis who were enrolled in DATATOP but subsequently determined not to have PD.[22]

INFORMED CONSENT

Subjects in the DATATOP study provided written, informed consent per the regulations of the local institutional review boards. The study procedures for this analysis were deemed to be exempt by the Emory University Institutional Review Board.

LABORATORY ANALYSIS OF 25(OH)D CONCENTRATIONS

Stored serum samples from the baseline and end point visits (or final visits for subjects who did not require levodopa therapy) were analyzed in blinded fashion by an enzyme-linked immunosorbent assay kit for $25(OH)D$ (IDS, Inc, Fountain Hills, Arizona). The limit of detection is 2.0 ng/mL. Individual samples were run in duplicate and batches of 40 to minimize interassay variability. Quality assurance for determination of $25(OH)D$ concentration was ensured by participation in the vitamin D external quality assessment scheme (DEQAS). The intra-assay and interassay coefficients of variation of the $25(OH)D$ enzyme-linked immunosorbent assay are less than 8.0% and less than 10.0%, respectively. Duplicate samples that had coefficients of variation greater than 10.0% were repeated. Based on $25(OH)D$ concentration cut points used in our clinical practice and reviewed by Holick,[1] we defined vitamin D insufficiency as a $25(OH)D$ concentration less than 30.0 ng/mL and vitamin D deficiency as a $25(OH)D$ concentration less than 20.0 ng/mL.

STATISTICAL ANALYSIS

We used SAS version 9.2 statistical software (SAS Institute, Inc, Cary, North Carolina) for all statistical analyses. Of the original 199 subjects randomized to the DATATOP placebo treatment arm, 170 had both baseline and end point/final blood draw samples available for analysis. Of these, 10 subjects were ulti-

Table 1. Cohort Demographic Characteristics and Prevalence of Vitamin D Insufficiency

Characteristic	Baseline Sample	End Point/Final Sample
Cohort		
Age, mean (SD) [range], y	61.0 (9.5) [34-78]	63.0 (9.8) [34-80]
UPDRS score, mean (SD) [range]	26.2 (12.1) [0-61]	42.4 (15.5) [9-82]
Hoehn and Yahr stage, mean (SD) [range]	1.7 (0.5) [1-2.5]	2.1 (0.6) [1-3]
Duration of PD, mean (SD) [range], y	1.9 (1.1) [0.2-5.4]	3.6 (1.5) [0.7-8.3]
BMI, mean (SD) [range]	26.1 (3.8) [18.3-38.4]	25.7 (3.9) [17.5-38.3]
All race/skin types, No. (%)	157 (100.0)	
White	152 (96.8)	
Black	4 (2.6)	
Hispanic	1 (0.6)	
Sex, No. (%)		
Male	101 (64.3)	
Female	56 (35.7)	
Serum sample collection, No. (%)		
Season		
Winter/spring, January-June	58 (36.9)	93 (59.2)
Summer/fall, July-December	99 (63.1)	64 (40.8)
Latitude		
≤32° N	20 (12.7)	
>32° N	137 (87.3)	

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); PD, Parkinson disease; UPDRS, Unified Parkinson's Disease Rating Scale.

mately determined to not have PD based on criteria described by Marras et al[22] (≥1 of the following clinical criteria: [1] investigator's confidence in the diagnosis of PD; [2] presence of atypical clinical features; [3] findings of imaging studies; [4] response to levodopa; and [5] results of autopsy examinations). Inspection of scatterplots revealed that the 25(OH)D concentration was more than 3 SDs above the mean for 3 samples. For the sample with the highest 25(OH)D concentration (95.5 ng/mL), the subject resided at the lowest latitude (25° N), was aged 70 years, and had data collected in October; such an extremely high 25(OH)D level suggests that the subject was either routinely sunbathing and/or had extraordinarily high vitamin D intake (either supplemental or dietary). For the other 2 outliers (with 25[OH]D concentrations of 80.1 and 76.7 ng/mL), the subjects were remarkably young (aged 37 and 47 years at baseline) and had their baseline visit during summer or fall months (July and September), again suggesting extreme deviations from the normal vitamin D intake and/or outside activity levels. Analysis conclusions did not differ when the data were analyzed with or without data from these 3 subjects. Owing to the suspected dietary and/or activity extremes for these subjects, data from these subjects were excluded from this analysis, leaving 157 DATATOP placebo-treated subjects with baseline and end point/final visit blood draws and probable PD.

Because 25(OH)D concentrations were approximately normally distributed, *t* tests were used to compare mean 25(OH)D concentrations between the summer/fall and winter/spring blood draws and between subjects residing above and below 32° N latitude (separately at the baseline and end point/final visits). Also, regression analysis was used to examine the associations between 25(OH)D concentration and latitude, age, and BMI (separately at the baseline and end point/final visits); similarly, logistic regression was used to examine the associations between the presence of vitamin D insufficiency and deficiency and these variables. To examine change in 25(OH)D concentration over time, raw change and annualized rate of change were analyzed. Annualized rate of change was calculated by taking the difference between end point/final and baseline concentrations and dividing by time interval (in years) between samples. A paired *t* test was used to examine the significance of the mean annualized rate of change. All statistical tests were performed using a 5% significance level (2-tailed).

RESULTS

SUBJECT DEMOGRAPHIC CHARACTERISTICS

Most participants were white (96.8%) and male (64.3%), with a mean (SD) BMI of 26.1 (3.8) at baseline (**Table 1**). The median interval between the baseline and end point/final samples was about a year (median, 13.0 months; interquartile range, 8-33 months); the distribution of these intervals was skewed (mean [SD], 18.9 [13.1] months). Most baseline samples were collected during the summer months, when 25(OH)D concentrations reach their annual maximum. In contrast, most end point/final visit samples were collected during the winter/spring months, when 25(OH)D concentrations typically reach a nadir.

VITAMIN D STATUS

At the baseline visit, a majority of subjects (69.4%) had vitamin D insufficiency and more than a quarter of subjects (26.1%) had vitamin D deficiency (**Table 2**). At the end point/final visit, these percentages fell to 51.6% and 7.0%, respectively, despite the fact that a higher percentage of the end point/final samples were collected during the winter/spring months.

CHANGES OVER TIME IN 25(OH)D CONCENTRATIONS

For most participants, 25(OH)D concentrations increased over the course of the study (mean [SD] raw change, 5.6 [11.1] ng/mL; 95% confidence interval [CI], 3.8-7.3 ng/mL; $P<.001$; mean [SD] annualized rate of

Table 2. Vitamin D Concentrations and Prevalence of Vitamin D Insufficiency

Vitamin D Status	Baseline Sample	End Point/Final Sample[a]
25(OH)D concentration, mean (SD) [range], ng/mL	26.3 (8.6) [8.4-59.8]	31.3 (9.0) [7.9-59.8]
Prevalence of vitamin D insufficiency, %[b]	69.4	51.6
Prevalence of vitamin D deficiency, %[b]	26.1	7.0
25(OH)D concentration stratified by season, mean (SD) [range], ng/mL		
Winter/spring	23.9 (7.8) [8.4-48.0]	30.5 (8.2) [10.1-53.7]
Summer/fall	27.7 (8.7) [11.5-59.8]	32.6 (10.0) [7.9-59.7]
25(OH)D concentration stratified by sex, mean (SD) [range], ng/mL		
Male	26.8 (8.5) [8.4-48.0]	30.7 (8.9) [7.9-54.6]
Female	25.4 (8.6) [13.2-59.8]	32.4 (9.2) [10.1-59.7]

Abbreviation: 25(OH)D, 25-hydroxyvitamin D.
SI conversion factor: To convert 25(OH)D to nanomoles per liter, multiply by 2.496.
[a] End point/final sample was the sample obtained at the study-defined end point/final visit.
[b] Vitamin D insufficiency was defined as a 25(OH)D concentration less than 30.0 ng/mL; vitamin D deficiency was defined as a 25(OH)D concentration less than 20.0 ng/mL.

change, 5.6 [13.9] ng/mL; 95% CI, 3.4-7.8 ng/mL; $P<.001$). Even when subjects who reached the end point before 6 months (n=29) were excluded (to reduce the potential artifact of inflation of the annualized rate of change), there was a mean increase in 25(OH)D concentration (mean [SD] annualized rate of change, 4.8 [9.4] ng/mL; 95% CI, 3.2-6.4 ng/mL; $P<.001$).

According to the DATATOP protocol, patients were required to either stop taking their current MVI supplement or switch to a study-supplied MVI; 24 subjects chose to take the study-supplied MVI supplements, but MVI use was not associated with an increase in 25(OH)D concentration from baseline to the final visit. Unexpectedly, the annualized rate of change was significantly higher in those subjects not taking the study-supplied MVI supplements (mean [SD], 6.3 [14.8] ng/mL) than in those subjects taking the study-supplied MVI (mean [SD], 1.7 [5.4] ng/mL) ($P=.01$). Although the number of subjects taking an MVI (n=24) was small, latitude did not appear to account for this finding. As expected, 25(OH)D concentrations at baseline were inversely correlated with age and latitude at baseline and end point/final visits. At end point visits, 25(OH)D concentrations and BMI were also inversely correlated; in contrast, at baseline visits, 25(OH)D concentrations demonstrated a slight positive correlation with BMI.

COMMENT

We observed high prevalences of vitamin D insufficiency (69.4%) and deficiency (26.1%) in subjects with early, untreated PD who were randomized to the placebo arm of the DATATOP study. Previous studies in Asian populations reported a higher prevalence of hypovitaminosis D (deficiency or insufficiency) in patients with more advanced disease,[19,23] suggesting that long-term effects of PD may contribute to the development of insufficient vitamin D concentrations. Contrary to our expectation that vitamin D levels might decrease over time because of disease-related inactivity and reduced sun exposure, vitamin D levels increased over the study period. These findings are consistent with the possibility that long-term insufficiency is present before

the clinical manifestations of PD and may play a role in the pathogenesis of PD.

Interestingly, the prevalences of deficiency and insufficiency for subjects in the early stages of PD (Hoehn and Yahr stages 1 and 2) were similar to but slightly higher than the prevalences we previously reported for patients with varying stages of PD (55.0% and 23%, respectively, for insufficiency and deficiency[20]). The DATATOP study protocol excluded patients taking high doses of vitamin supplements (including vitamin D); this exclusion may help explain the higher prevalence of vitamin D insufficiency reported here than in our previous clinical research cohort.[20] Also, the subjects in this DATATOP cohort were more widely distributed across latitudes in the United States, whereas subjects in our previous study were from the southeastern United States, increasing the generalizability of our results and offering a further explanation for the slightly higher prevalence observed in this analysis.

However, vitamin D deficiency (25[OH]D concentration <20.0 ng/mL) at baseline in our cohort was less prevalent than reported for Asian cohorts—about half as prevalent as reported by Sato et al[19] in a small cohort of patients with early PD from Japan (N=20; 9 males, 11 females) in which 45% were deficient using the same criterion. The mean baseline 25(OH)D concentration for our cohort (26.3 ng/mL; 95% CI, 24.9-27.5 ng/mL) was also slightly higher than that reported by Sato and colleagues in 2 small cohorts of subjects with early PD (Hoehn and Yahr stages 1 and 2), one of men and women (mean, 22 ng/mL; 95% CI, 18-25 ng/mL; N=20)[19] and a second of women with PD (mean, 17 ng/mL; 95% CI, 16-18 ng/mL; N=26).[24] Differences in age, ethnicity, and sex could account for the more optimal vitamin D concentrations seen in our cohort. The mean age in our cohort was about 10 years younger than the mean age in the previous reports by Sato et al,[19,24] confirming that older individuals tend to have lower serum 25(OH)D concentrations than younger individuals. People of Asian ancestry tend to have darker skin tones than would be expected in our predominantly white DATATOP cohort, and dark-skinned individuals tend to have lower vitamin D concentrations than lighter-skinned individuals. Also, women in the United States tend to have slightly lower vitamin D concentrations than men,[25] which is another pos-

sible explanation for the observed differences in sex; the DATATOP cohort was predominantly male (64.3%), while the cohort in the study by Sato et al[19] was predominantly female (55.0%). Finally, the Asian cohort included subjects with dementia, which is also associated with low vitamin D concentrations. Thus, population characteristics could explain observed differences in prevalence compared with previously reported cohorts.

Also consistent with our previous finding,[20] the mean 25(OH)D concentration in DATATOP participants appears to be lower than that reported for the general population (mean, 26.8 ng/mL for men and 25.4 ng/mL for women in the DATATOP cohort vs 30 ng/mL [95% CI, 31-32 ng/mL] and 26 ng/mL [95% CI, 26-27 ng/mL] for non-Hispanic white men and women aged ≥60 years, respectively, in the Third National Health and Nutrition Examination Survey,[25] completed between 1988 and 1992). One of the 2 previous studies[19,24] reporting vitamin D concentrations in patients with early PD also reported that 25(OH)D concentrations were significantly lower in patients with early PD than in healthy control subjects.[24] In the second study,[19] 25(OH)D concentrations in patients with early PD were similar to those in healthy control subjects, but as we have discussed, the small cohort size (only 20 patients with early PD and 33 control subjects), lack of sex matching, and inclusion of subjects with dementia make comparisons with this second study problematic. A third report also noted that 25(OH)D concentrations were significantly lower in patients with PD than in age-matched control subjects[26] but did not report the Hoehn and Yahr staging for the patients with PD and used a vitamin D analysis technique that may not be reliable.[27] While the DATATOP study did not include control subjects without PD, the current findings are compatible with the notion that vitamin D insufficiency is more common in patients with PD and is present early in the course of the disease, before patients are significantly disabled.

The observed mean increase in 25(OH)D concentration over the study period, albeit small, is notable because we expected either no change or a decrease in concentration. This increase cannot be explained on the basis of known or predicted confounding variables such as season, latitude, and BMI. It is unlikely that sample degradation contributed to this difference because vitamin D concentrations are known to be remarkably stable over time, with prolonged periods at room temperature, and after undergoing multiple freeze-thaw cycles.[28,29] It is also unlikely that seasonal variation could explain the finding because, as noted earlier, most baseline samples were drawn in the summer/fall months when vitamin D levels typically reach their yearly maximum, yet most of the end point/final samples were drawn in the winter/spring months. One would thus expect the 25(OH)D levels to decrease, not increase, from baseline to the end point/final visit. Another potential explanation for the observed increase is that 15.9% of the cohort reported taking MVI supplements containing 400 IU of vitamin D; based on a study by Heaney et al,[30] the expected change in 25(OH)D concentration from taking supplemental vitamin D is about 0.3 ng/mL per 40 IU of vitamin D in an oral supplement, or 3 ng/mL per 400 IU. However, this

seems unlikely to account for the findings because only 24 participants elected to take study-supplied MVI supplements, and the annualized rate of change was actually higher in the subjects who did not take the MVI supplements. Per DATATOP inclusion criteria, patients could take no more than 400 IU of vitamin D (as part of an MVI) in the month prior to their baseline visit, and we can identify with certainty only those subjects who were taking an MVI at the time of the study baseline. Recent studies have noted that about half of patients with PD take MVI supplements,[31] so the number of people taking up to 400 IU of vitamin D prior to entry into the DATATOP study may have been higher (closer to 50%); if so, then we would again anticipate a negative annualized rate of change for 25(OH)D concentration. It is also possible that unbeknownst to study coordinators, subjects began taking over-the-counter vitamin D supplements in violation of the study protocol. Finally, one could argue that disease progression might subtly decrease a subject's outdoor activity levels from the baseline visit (when they did not need symptomatic therapy) to the end point/final visit (after which symptomatic therapy was initiated); this would be expected to result in either no change or a decrease in 25(OH)D concentration rather than the observed increase. Despite an unclear explanation for the increase in 25(OH)D concentrations, we can conclude from our findings that vitamin D status does not appear to deteriorate during the early disease stage of PD.

A strength of our study is that, to our knowledge, the study cohort is the largest and most well-characterized cohort of patients with PD in whom vitamin D status has been investigated. In addition, diagnostic accuracy in early PD ranges from 75%[32] to 90%[33]; in this cohort, the diagnosis of PD for subjects was confirmed based on their subsequent clinical course and reported to be greater than 90%.[22,33] Unfortunately, while samples from the DATATOP cohort allow analysis of vitamin D concentrations at an early stage of the disease, there are no matched control subjects who can be directly compared with this cohort.

We confirm a high prevalence of vitamin D insufficiency in patients with recent onset of PD, during the early clinical stages in which patients do not require symptomatic therapy. Furthermore, vitamin D concentrations did not decrease but instead increased slightly over the course of follow-up. This provides evidence that during early PD, vitamin D concentrations do not decrease with disease progression. Future studies are needed in presymptomatic or at-risk subjects to clarify the natural history of vitamin D concentrations with respect to onset of PD-related symptoms as well as the potential role of vitamin D insufficiency or deficiency in the pathogenesis or progression of PD.

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