Author's response to reviews

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Age-related increases in parathyroid hormone may be antecedent to both osteoporosis and dementia: a clinical study

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Abstract

Background: Numerous studies have reported that the age-induced increase in serum parathyroid hormone (PTH) levels is associated with cognitive decline and loss of bone mineral density (BMD). However, little is known about the correlation that may exist between processing speed, cognition and BMD in cases of elevated PTH. Since we have found in earlier experiments that P300 latency is an early measure and a better predictor of preclinical dementia than memory or mental status tests, we decided to determine if there are any significant correlations between serum PTH levels, processing speed and/or BMD.

Methods: The serum PTH levels of the recruited subjects who met the inclusion/exclusion criteria (n=92, age-matched, age 18-90 years, mean=58.85, SD=15.47) were measured and these levels were statistically correlated with event-related P300 potentials. Groups were compared for age, BMD and P300 latency. One-tailed tests were used to ascertain the statistical significance of the correlations.

Results: The study groups were categorized and analyzed for differences of PTH levels: PTH levels <30 (n=30, mean = 22.7±5.6 SD) and PTH levels >30 (n=62, mean = 62.4±28.3 SD, p≤.02). Patients with PTH levels <30 showed statistically significantly less P300 latency (P300= 332.7 ±4.8 SE) relative to those with PTH levels >30, which demonstrated greater P300 latency (P300=345.7 ±3.6 SE, p=.02).

Participants with PTH values <30 (n=26) were found to have statistically significantly higher BMD (M=-1.25 ±.31 SE) than those with PTH values >30 (n= 48, M= -1.85 ±.19 SE, p=.04).

Conclusion: Our findings of a statistically lower BMD and prolonged P300 in patients with high PTH levels may suggest that elevated plasma PTH coupled with prolonged P300 latency may become putative biological markers of both dementia and osteoporosis. This study provides the first potential evidence for the importance of neural processing speed as an early electrophysiological marker for osteoporosis, which may support a direct link between osteoporosis and cognitive decline and warrants further investigation.

Key words: P300, hyperparathyroidism, dementia, osteoporosis, aging, calcium, vitamin D.
**Introduction**

Parathyroid hormone (PTH) is anabolic in bone, but when secreted in excess it is catabolic [1]. Its levels increase with age in both genders, paralleling the incidence of osteopenia and osteoporosis [2]. It has recently been discovered that intermittent administration of recombinant human PTH 1-34 (teriparatide) suppresses endogenous PTH production, possibly via negative feedback [3], and teriparatide is now being used as a treatment for osteoporosis. As an osteoporosis treatment, teriparatide administration has been shown to stimulate bone formation and increase bone mineral density [4].

Our greater understanding of PTH has led to lowering of the reference ranges. In 2003, the American Kidney Foundation recommended that levels should be kept between 35 and 70 pg/ml [5] for stage 3 chronic kidney disease (CKD), which is characterized by a glomerular filtration rate (GFR) of 30-59 mL/min/1.73m², that an estimated 7.7 % of the population suffers [6]. Currently, the acceptable reference range for parathyroid hormone (PTH) is between 10 and 60 pg/mL. It has been suggested that, where there is normal renal function and elevated serum calcium, an intact PTH concentration of >50 pg/mL strongly suggests primary hyperparathyroidism [7]. It is well established [8] that hyperparathyroidism is responsible for changes in bone metabolism leading to a reduction in bone mineral density.

While numerous studies have reported that age-induced increased plasma PTH levels are associated with cognitive decline [9, 10], little is known about the correlation that may exist between processing speed and bone density in cases of elevated PTH. To date only one study has attempted to correlate PTH levels with P300 latency (a measure of processing speed) [11].

The P300 wave is an event related potential that can be recorded via EEG as a positive deflection in voltage at a latency of roughly 300 + age milliseconds [12]. The presence, magnitude, topography, and time of this signal can measure processing speed. Prolonged P300 latency is an antecedent to memory loss and cognitive decline [12]. Since hyperparathyroidism has already been associated with cognitive decline [9, 10] and increased P300 latency [11] is an early measure and a better predictor of preclinical dementia than memory or mental status tests [12], we decided to determine if PTH levels correlate to processing speed.
and/or bone mineral density (BMD) over a broad age range based on the clinical guidelines set forth by the National Osteoporosis Foundation for diagnosing osteoporosis based on BMD [13].

**METHODS**

*Participants*

The sample consisted of 95 patients participating in the Path Medical program. Ages ranged between 18 and 90 years, with a mean of $M = 58.85, SD = 15.47$. We started with age 18 because many individuals enter adulthood with poor bone density. Furthermore, osteoporosis is now considered by the National Osteoporosis Foundation to be a childhood disease [14, 15]. Missing data reduced the sample size for P300SP and P300V to 92. For BMD, missing data reduced the sample size to 74. Forty (forty-two percent) were male and fifty-six (fifty-eight percent) were female.

*Measurements*

In this study, analysis was conducted only on patients with complete data and (n=92, age-matched, age 18-90 years, mean=58.85, SD=15.47) had intact serum PTH levels measured between 9 AM and 3 PM compared to brain speed as measured by P300 latency. The P300 wave is an event related potential that can be recorded via electroencephalograph (EEG) as a positive deflection in voltage at a latency of roughly 300 msec. We have found in previous research that the P300 wave is an accurate predictor of cognitive decline [4], and the “reference” range for P300 latency is roughly 300 + age msec. In this study, groups were categorized by patients with: PTH levels <30 (n=30, mean = 22.7±5.6 SD) and PTH levels >30 (n=62, mean = 62.4±28.3 SD, $p \leq .02$). BMD was measured by a dual energy X-ray absorptiometry (DEXA) scan. Groups were compared for age, BMD and P300 latency

*Statistical Analysis*

One-tailed tests were used to ascertain the statistical significance of the correlations. The statistical analysis of the data was conducted in four phases. First, the PTH measure was dichotomized, with PTH values below 30 categorized as 1 (low), and PTH values above 30 categorized as 2 (high). We used 30 as the
cutoff since it is close to but slightly lower than the midpoint of the current reference range (35), and since 30 is clearly well below the current risk range which is not yet well defined. This step was taken to test the statistical significance of differences in P300P, P300V and BMD between low and high levels of PTH. In addition, the BMD measure was dichotomized using a median (Md) split procedure (Md = -1.88), with BMD values equal to or lower than Md categorized as 1 (low), and values greater than Md categorized as 2 (high). This step was taken to test the statistical significance of differences in P300P and P300V, between low and high levels of BMD.

The second phase of the analysis of the data involved the calculation of the q-test of normality for P300SP, P300V, BMD and age. This test was conducted to determine whether parametric or non-parametric tests of significance should be used to examine differences between the high and low levels of PTH on P300SP, P300V and BMD—and between the high and low levels of BMD on P300SP and P300V. A test of normality was also conducted for PTH.

The q-test is calculated by dividing the sample’s standard deviation into the sample’s range. The obtained q statistic is compared against a given range for the sample size at hand, and a q value falling within this range, derived on the basis of a .025 significance level [16] is interpreted as indicative that the sample distribution does not depart statistically significantly from normality. A table due to Sachs (1984) [17] provides critical ranges of values for varying sample sizes. For the present sample size of 95 for age, the q span, ranged between 4.17 and 6.07; for the P300SP and P300V sample size of 92, it ranged between 4.15 and 6.05; and for BMD’s sample size of 74, it ranged between 4 and 5.87.

The third phase of the analysis of the data involved the calculation of the correlations among age, BMD, PTH, P300SP, and P300V.

The fourth phase of the analysis of the data involved the calculation of tests of statistical significance using the dichotomized PTH measure as the independent variable and P300SP, P300V, BMD, and age as dependent variables. Tests of statistical significance were also calculated using the dichotomized BMD measure as the independent variable and P300SP and P300V as the dependent variables. The effect sizes
(ES) of the categorized PTH and BMD measures were calculated to ascertain the strength of association between the categorized independent and the dependent variables. Effect size is calculated as

\[ ES = \left(\frac{t^2}{t^2 + df}\right)^{1/2}. \]

An ES equal to or higher than .20 is considered empirically consequential.

**Results**

The following paragraphs describe the outcomes of the tests of normality, the correlational analyses, and the analyses of differences between the levels of the dichotomized forms of PTH and BMD.

**Tests of Normality**

Figures 1 to 5 display the distributions of P300SP (latency, in milliseconds), P300V, BMD, PTH and age. For P300SP, P300V (Voltage), BMD and age, the distributions tended to approach symmetry, suggesting further, more formal testing for normality by means of the \( q \)-test.

Table 1 displays the \( q \)-test outcomes. As shown in this table, the \( q \) value of P300SP was 6.02, that for P300V was 5.23, and that for age was 5.04—all falling within the normality range for \( n = 92 \) of 4.15 to 6.05. For BMD, it was 5.54, falling within the normality range for \( n = 74 \) of 4 to 5.87. The \( q \) value for PTH was 6.38, falling outside the 4.17 to 6.07 normality range for \( n = 95 \). These outcomes supported the assumption of normality required for the use of parametric tests in the case of P300SP, P300V, BMD, and age, and hence, the Pearson correlation coefficient was used to calculate the level of relation among the variables in continuous form, and the \( t \)-test was used to ascertain the statistical significance of the
differences between the two categories of PTH on P300SP, P300V, BMD. Since the hypotheses were stated unidirectionally, one-tailed tests were used; alpha (α) was set at the .05 level.

Table 1. q-Tests for Normality of Distribution. The q range for normality for a sample size of 93, as was the case for P300SP, P300V, PTH, and Age, is 4.16 to 6.07 with a significance level of .025. For a sample size of 74, as was the case for Bone density, the q range is 4 to 5.87, also with a significance level of .025.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Statistics</th>
<th>P300SP</th>
<th>P300V</th>
<th>BMD</th>
<th>PTH</th>
<th>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>SD</strong></td>
<td>28.07</td>
<td>2.66</td>
<td>1.41</td>
<td>30.01</td>
<td>15.47</td>
</tr>
<tr>
<td></td>
<td><strong>Range</strong></td>
<td>169</td>
<td>13.93</td>
<td>7.82</td>
<td>191</td>
<td>78</td>
</tr>
<tr>
<td></td>
<td><strong>q</strong></td>
<td>6.02</td>
<td>5.23</td>
<td>5.54</td>
<td>6.37</td>
<td>5.04</td>
</tr>
</tbody>
</table>

**Pearson Correlation Coefficients**

Table 2 displays the Pearson correlation coefficients. In this table, BMD and PTH appear in both continuous and dichotomized form. As evidenced by the outcomes shown in this table, age proved to be statistically significantly correlated with PTH, P300SP, and P300V; BMD proved to be statistically significantly correlated with PTH in dichotomized form; BMD in dichotomized form proved to be statistically significantly correlated with P300V; PTH proved to be statistically significantly correlated with P300P; and P300SP proved to be statistically significantly correlated with P300V.
Table 2. Correlation Matrix.

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Age</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. BMD</td>
<td>.03</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. BMD&lt;sup&gt;1&lt;/sup&gt;</td>
<td>.01</td>
<td>.62*</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. PHT</td>
<td>.22*</td>
<td>-.04</td>
<td>-.03</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. PTH&lt;sup&gt;2&lt;/sup&gt;</td>
<td>.21*</td>
<td>-.21*</td>
<td>-.11</td>
<td>.62*</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. P300SP</td>
<td>.40*</td>
<td>-.07</td>
<td>-.04</td>
<td>.18*</td>
<td>.22*</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>7. P300V</td>
<td>-.18*</td>
<td>-.15</td>
<td>-.28*</td>
<td>-.06</td>
<td>.00</td>
<td>-.19*</td>
<td>1</td>
</tr>
</tbody>
</table>

P< 0.05

<sup>1</sup> Dichotomized (1 <= -1.88; 2 > -1.88) <sup>2</sup>Dichotomized (1 < 30; 2 > 30)

Tables 3 to 7 depict the t-test outcomes. They show the means, standard deviations and standard errors of the dependent variables for each category of the independent variables, and show the t-statistics, p-values, and effects sizes.

Table 3 displays the t-test outcomes of P300SP by PTH in categorized form. As shown in this table, the P300SP mean of the low category of PTH (M = 332.66, SD = 6.39) proved to be statistically significantly lower than that of the high PTH category (M = 345.68, SD = 28.08), t = -2.12, df = 90, p = .02 (1-tail test). The effect size was ES = .22—an effect which, being greater than .20, proved to have practical significance according to criteria propounded by Cohen [18] and Kirk [19].
These findings disclosed that level of PTH is positively associated with level of P300P, and that the
strength of the association is of practical importance. The implications of these findings are discussed
below.

Table 3. *t*-Test of the Difference in P300SP Between the Categories of PTH.

<table>
<thead>
<tr>
<th>PTH</th>
<th>P300SP</th>
<th>t-Test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>M</td>
</tr>
<tr>
<td>1 (&lt; 30)</td>
<td>30</td>
<td>332.66</td>
</tr>
<tr>
<td>2 (&gt; 30)</td>
<td>62</td>
<td>345.68</td>
</tr>
<tr>
<td>Total</td>
<td>92</td>
<td>341.44</td>
</tr>
</tbody>
</table>

*Effect size

Table 4 displays the *t*-test outcomes of P300V by PTH in categorized form. As shown in this table, the
P300V mean of the low category of PTH (*M* = 5.27, *SD* = 3.15) did not differ statistically significantly
from that of the high PTH category (*M* = 5.28, *SD* = 2.39), *t* = -.028, *df* = 53.1, *p* = .49 (1-tail test). The
effect size was *ES* = .03, showing a null effect of PTH on P300V. These findings disclosed a lack of
association between PTH and P300V levels. The implications of these findings are also discussed below.

Table 4. *t*- Test of the Difference in P300V Between the Categories of PTH.

<table>
<thead>
<tr>
<th>PTH</th>
<th>P300V</th>
<th>t-Test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>M</td>
</tr>
<tr>
<td>1 (&lt; 30)</td>
<td>30</td>
<td>5.27</td>
</tr>
<tr>
<td>2 (&gt; 30)</td>
<td>62</td>
<td>5.28</td>
</tr>
</tbody>
</table>
Table 5 displays the \( t \)-test outcomes of BMD by PTH in categorized form. As shown in this table, the mean BMD score of participants in the low category of PTH (\( M = -1.25, SD = 1.57 \)) differed statistically significantly from that of participants in the high PTH category (\( M = -1.85, SD = 1.28 \)), \( t = 1.77, df = 72, p = .04 \) (1-tail test). The effect size was \( ES = .20 \), showing a substantive effect of PTH on BMD in terms of criteria propounded by [18] and [19]. These findings disclosed an empirically important association between levels of PTH and levels of BMD. The implications of these findings are also discussed below.

### Table 5. \( t \)- Test of the Difference in BMD Between the Categories of PTH.

<table>
<thead>
<tr>
<th>PTH</th>
<th>BMD</th>
<th>( t )-Test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( N )</td>
<td>( M )</td>
</tr>
<tr>
<td>1 (&lt; 30)</td>
<td>26</td>
<td>-1.25</td>
</tr>
<tr>
<td>2 (&gt; 30)</td>
<td>48</td>
<td>-1.85</td>
</tr>
<tr>
<td>Total</td>
<td>74</td>
<td>-1.64</td>
</tr>
</tbody>
</table>

*Effect size
Table 6 displays the \( t \)-test outcomes for P300SP by BMD in categorized form. As shown in this table, the mean age of participants in the low category of BMD (\( M = 344.18, SD = 30.40 \)) did not differ statistically significantly from that of participants in the high PTH category (\( M = 341.99, SD = 21.48 \)), \( t = .35, df = 70, p = .36 \) (1-tail test). The effect size was \( ES = .04 \)—an effect which, being lower than .20, proved to have insubstantial practical significance according to criteria propounded by [18] and [19]. This effect was the same as the Pearson correlation coefficient of P300SP with the original categorized BMD scores (\( r = -.04, p > .05 \)). The implications of these findings are also discussed below.

Table 6. \( t \)-Test of the Difference in P300SP Between the Categories of BoneD.

<table>
<thead>
<tr>
<th>BMD</th>
<th>( N )</th>
<th>( M )</th>
<th>( SD )</th>
<th>( SE )</th>
<th>( t )</th>
<th>( df )</th>
<th>( p )</th>
<th>( ES^* )</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (&lt;-1.88)</td>
<td>36</td>
<td>344.18</td>
<td>30.40</td>
<td>5.06</td>
<td>( .35 )</td>
<td>70</td>
<td>.36</td>
<td>.04</td>
</tr>
<tr>
<td>2 (&gt;1.88)</td>
<td>36</td>
<td>341.99</td>
<td>21.48</td>
<td>3.58</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>92</td>
<td>341.44</td>
<td>28.07</td>
<td>2.93</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Effect size

Table 7 displays the \( t \)-test outcomes for P300V by BMD in categorized form. As shown in this table, the mean age of participants in the low category of BMD (\( M = 5.80, SD = 2.83 \)) differed statistically significantly from that of participants in the high BMD category (\( M = 4.38, SD = 13.66 \)), \( t = 2.46, df = 70, p = .005 \) (1-tail test). The effect size was \( ES = .28 \)—an effect which, being greater than .20, proved to have practical significance. This effect was the same as the Pearson correlation coefficient of P300SP with the
original categorized BMD scores ($r = -.28$, $p = .008$). The implications of these findings are also discussed below.

Table 7. *-Test of the Difference in P300V Between the Categories of BMD.

<table>
<thead>
<tr>
<th>BMD</th>
<th>P300V</th>
<th></th>
<th></th>
<th></th>
<th>df</th>
<th>p</th>
<th>ES*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>M</td>
<td>SD</td>
<td>SE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (&lt;=-1.88)</td>
<td>36</td>
<td>5.80</td>
<td>2.83</td>
<td>.47</td>
<td>2.46</td>
<td>70</td>
<td>.005</td>
</tr>
<tr>
<td>2 (&gt;1.88)</td>
<td>36</td>
<td>4.38</td>
<td>13.66</td>
<td>.33</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>92</td>
<td>5.28</td>
<td>2.66</td>
<td>.28</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Finally, table 8 displays the means, standard deviations and standard errors of the two PTH categories. As shown in this table, the two categories’ means differed substantially: category 1 (low): $M = 22.65$; category 2 (high): 62.37.

Table 8. Means and Standard Deviations of PTH by the Two PTH categories.

<table>
<thead>
<tr>
<th>Category</th>
<th>N</th>
<th>M</th>
<th>SD</th>
<th>SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (&lt; 30)</td>
<td>30</td>
<td>22.65</td>
<td>5.62</td>
<td>1.03</td>
</tr>
<tr>
<td>2 (&gt; 30)</td>
<td>65</td>
<td>62.37</td>
<td>28.33</td>
<td>3.51</td>
</tr>
<tr>
<td>Total</td>
<td>95</td>
<td>46.82</td>
<td>30.01</td>
<td>3.08</td>
</tr>
</tbody>
</table>
Discussion

Our findings suggest that age dependent prolonged P300 latency, as well as age dependent increased PTH levels, may interact. This is a timely discovery since there has been a recent explosion of research highlighting the connections between the brain and the bones, and a new field has been birthed called neuropsychosteology [20, 21]. Many studies have confirmed neuropsychiatric disease increases with osteoporosis [22, 23, 24].

Based on our findings, we suggest that control of PTH levels may be important for protecting against age-induced dementia. This study provides the first potential evidence for the importance of processing speed as an early electrophysiological marker of OP, which warrants further investigation.

Moreover, OP is a genetic disease and as such the role of 1,25-dihydroxyvitamin D$_3$ receptor gene polymorphisms, known OP genetic antecedents [25] may contribute in some way to the age-linked impairments in both parathyroid and brain speed functioning. It is to be noted that PTH tides are of short duration while Vitamin D or calcitriol tides are of long duration. PTH is quick in mobilizing bone calcium, while calcitriol tends to increase the absorption of dietary calcium. In the case of low or no dietary calcium, calcitriol mobilizes bone calcium and thus increases parathyroid initiation and demineralization; therefore mixed effects occur during Vitamin D deficiency, and psuedo or secondary hyperparathyroid conditions occur. Furthermore, overnight fasting with reduced absorption of dietary calcium associated with age results in a regulatory set point inducing an increase of PTH secretion with age. PTH bursts decrease with age as blood levels generally increase with age. These trends are associated with dementia and aging. [26].

It is apparent that PTH levels should be kept below 60 pg/ml, and we believe based on our findings that these levels may be lowered still. Further research should involve P300 latency testing for a larger number of patients and stratification by age, and correlating PTH levels and BMD.

Increases in PTH levels and age are major factors responsible for age-related increase in bone resorption, and contribute to kidney stone formation, polyuria, hypertension, constipation, fatigue, and elevated serum
and urine calcium [27]. PTH levels need to be monitored in osteoporotic, memory-impaired people and lowering the levels may be an important part of the therapeutic process of teriparitide injections. At the PATH Medical Clinic, PTH levels were reduced by teriparitide injections by an average of 20 points, possibly due to a negative feedback mechanism. This is further supported by others [3]. Additional research has shown that teripartide therapy may need to be supplemented by GH or GH-dependent factors in order for the anabolic response of bone [28].

Finally, the findings of this study showing a significant relationship between higher PTH plasma levels and prolonged P300 latency as well as a decrease in BMD suggest that hyperparathyroidism due in part to age may lead to dementia and OP. Further studies are warranted to confirm the value of increased PTH levels coupled with increased P300 latency as putative biological markers of both dementia and OP.

**Conclusion**

Patients with PTH levels <30 showed statistically significantly lesser P300 latency (P300= 332.7 ± 4.8 SE) relative to those with high PTH levels (>30), who demonstrated greater P300 latency (P300=345.7 ± 3.6 SE, p=.02). In addition, participants with PTH values <30 (n=26) were found to have statistically significantly higher bone density (M=-1.25 ± .31 SE) than those with PTH values >30 (n= 48, M= -1.85 ± .19 SE, p=.04)

Our findings of a statistically lower bone density and prolonged P300 latency in patients with high PTH levels may suggest that PTH levels coupled with delayed P300 latency may become putative biological markers of not only dementia but OP. We await further confirmation of this first preliminary study.

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Conflict of interest statement: We declare that we have no conflict of interest. Eric R. Braverman MD, is the director of PATH Clinics where he utilizes both the P300 and TOVA as diagnostics, and Kenneth Blum, PhD is the scientific director of the PATH Research Foundation and is a paid consultant.

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