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Memory, Mood, and Vitamin D in Persons with Parkinson's Disease

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Abstract

Background—Research in recent years has suggested a role of vitamin D in the central nervous system. The final converting enzyme and the vitamin D receptor are found throughout the human brain. From animal studies vitamin D appears important in neurodevelopment, up-regulation of neurotrophic factors, stabilization of mitochondrial function, and antioxidation.

Objective—To examine the relationship between serum vitamin D and neuropsychiatric function in persons with Parkinson's disease (PD).

Methods—This is an add-on study to a longitudinal study following neuropsychiatric function in persons with PD. Baseline neuropsychiatric performance and serum 25-hydroxyvitamin D were examined for 286 participants with PD. Measures of global cognitive function (MMSE, MOCA, Mattis Dementia Scale), verbal memory (Hopkins Verbal Learning Test), fluency (animals, vegetables, and FAS words), visuospatial function (Benton Line Orientation), executive function (Trails Making Test and Digit-Symbol Substitution), PD severity (Hoehn & Yahr and Unified Parkinson's Disease Rating Scale) and depression (Geriatric Depression Scale (GDS)) were administered. Multivariate linear regression assessed the association between vitamin D concentration and neuropsychiatric function, in the entire cohort as well as the non-demented and demented subsets.

Results—Using a multivariate model, higher vitamin concentrations were associated with better performance on numerous neuropsychiatric tests in the non-demented subset of the cohort. Significant associations were specifically found between vitamin D concentration and verbal fluency and verbal memory ($t = 4.31$, $p < 0.001$ and $t = 3.04$, $p = 0.0083$). Vitamin D

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concentrations also correlated with depression scores ($t = -3.08$, $p = 0.0083$) in the non-demented subset.

Conclusions—Higher plasma vitamin D is associated with better cognition and better mood in this sample of PD patients without dementia. Determination of causation will require a vitamin D intervention study.

Keywords

Parkinson's disease; vitamin D; dementia; depression; cognition

INTRODUCTION

Parkinson's disease (PD) is characterized clinically by the following motor symptoms: bradykinesia, resting tremor, rigidity, and impaired postural responses. In addition there are non-motor features that are common and often times extremely debilitating. About 30% of persons with PD suffer from cognitive impairment and dementia [1, 2]. Dementia is associated with nursing home placement and shortened life expectancy in persons with PD [3, 4]. Intervening in the development of dementia has the potential to improve morbidity and mortality in persons with PD. Thus far dementia treatments for PD have shown underwhelming results [5].

Vitamin D's role in health first surfaced during the industrial revolution when rickets appeared as an epidemic in temperate climates. In the last decade the theoretical role of vitamin D in health has greatly expanded. Data demonstrate that low vitamin D increases the risk of type 2 diabetes mellitus, multiple sclerosis, hypertension, cancer, and infections [6]. Vitamin D receptors are present in the prostate, breast, colon, kidney, immune cells, and the brain [6]. In the human brain the final converting enzyme for vitamin D was demonstrated in all 13 regions examined and its receptor (VDR) in all but one region (the basal forebrain) [7]. The degree of immunoreactivity varied in the specific hippocampal regions, but most stained moderately or intensely for the enzyme and receptor [7]. The amygdala had less intense staining; weak for the receptor and moderate for the enzyme [7].

Studies looking at the relationship between vitamin D and cognition have been largely cross sectional and somewhat inconsistent. A 2012 meta-analysis concluded that lower vitamin D levels are associated with poorer cognitive function and higher risk of Alzheimer's disease [8]. There are very few intervention studies that have looked at cognition. One in institutionalized elderly found an improvement in cognitive function in a subset of their subjects (those with BMI less than 24.4 kg/m2 at baseline) [9]. Another that focused on young persons (average age 22) did not show an effect on cognition or mood [10]. A number of cross–sectional studies have shown relationships between serum vitamin D concentrations and selfreported mood in persons without PD [11–13]. An interventional study in Norway showed an improvement in depression symptoms in persons placed on weekly vitamin D supplementation for a year [14]. To our knowledge, there are no published studies on the association between vitamin D concentration and neuropsychological function in a large population with PD. We designed this analysis to test the hypothesis that vitamin D concentrations have a relationship with neuropsychological function (mood and memory) in a PD cohort.

MATERIALS AND METHODS

This is an add-on study to a longitudinal study following neuropsychiatric function in persons with PD [15]. Participants were recruited through the Parkinson's Disease Research, Education, and Clinical Center at the Portland and Puget Sound Veteran Affair (VA)

Clinics. TheHumanSubjects Institutional Boards of the VA Puget Sound, the University ofWashington, and the PortlandVAapproved the study. All individuals provided informed consent and underwent evaluation including a medical history, a general neurological examination, examination of PD severity using the Unified Parkinson's Disease Rating Scale motor section (UPDRSm) and Hoehn andYahr Scale (H&Y) [16, 17], laboratory tests, and neuropsychological assessments. All testing and blood draws were completed on the same day. All subjects fulfilled the United Kingdom Brain Bank clinical criteria for PD as determined by a movement disorders specialist [18].Aconsensus panel determined the presence or absence of dementia based on the criteria in the Diagnostic and Statistical Manual of American Psychiatric Association (4th edition) [19].

Persons with PD were enrolled [18]. Not all participants were Veterans, as non-Veterans could also be enrolled. Of the original 307 subjects in the Udall dataset, 12 were excluded due to a diagnosis other than PD while an additional 9 were excluded due to missing data from the control variables in the models.

Measures

Baseline cognitive tests and serum 25-hydroxyvitamin D measured by radioimmunoassay were examined for 286 participants with PD. Measures of global cognitive function (Mini Mental Status Exam (MMSE) [20], Montreal Cognitive Assessment (MoCA) [21], Mattis Dementia Scale [22]), verbal memory (Hopkins Verbal Learning Test [23]), semantic verbal fluency (number of animals, vegetables, and words starting with F, A, and S that can be given in one minute), visuospatial function (Benton Line Orientation [24]), executive function (Trails Making Test [24] and Digit Symbol Substitution [25]), and depression (Geriatric Depression Scale (GDS) [26]). Vitamin D concentration of <20 ng/ml were considered insufficient ≥20 ng/ml – <30 ng/ml deficient, and >30 ng/ml sufficient [6]. As this was an addon study explicit data on vitamin D supplementation was not collected during the assessments.

Statistical analysis

Principle analysis used direct multivariate multiple linear regression to assess the association between vitamin D and cognitive function. Relationships between vitamin D concentrations and the cognitive tests were examined in the entire cohort (n = 286) as well the non-demented and demented subsets of the cohort (n = 225 and n = 61 respectively). All comparisons were corrected for age, disease duration, and disability according to Hoehn & Yahr (H&Y) score. These covariates were selected based on the known relationships of cognitive ability with age and to control confounding according to the observed relationships between vitamin D and age, disease duration, and severity [27]. Exploratory data analysis included simple linear correlation of the outcome variables with vitamin D and comparison of background demographics and neuropsychiatric outcomes between demented and non-demented subjects using Student's t-tests.

Given the large number of response variables and to account for the multiple comparisons between vitamin D and the cognitive tests, a Holm-Bonferroni stepwise correction was applied to the sets of p-values from the multiple regression models. Linear correlations between vitamin D and the cognitive tests both before and after multivariate model adjustment were similarly corrected for multiple comparisons.

Model integrity was evaluated using standard diagnostic procedures for linear regression models. Potential outliers and leverage points were identified using a combination of Cook's Distance and visual inspection of the residual plots. Normality of the outcome sets was evaluated using Q-Q plots comparing the observed probability quantiles of the data against

the expected quantiles of the normal probability cumulative distribution function. Homogeneity of the error variance was evaluated visually using plots of model residuals against the predicted responses. All diagnostic procedures were done iteratively to verify consistency and robustness of the adjusted models.

The relationship between vitamin D and cognitive measures was further examined for causal mediation due to mood as measured by GDS score. Models for mediation and outcome were taken from the same multivariate linear regression models described above. The analysis utilized covariate corrected vitamin D3 as the independent variables, GDS score as the mediator, and the significant cognitive tests as the outcomes. Variance estimation of the average causal mediation was done using bootstrapping with 10,000 sampling iterations per model to guarantee robustness of the results. All statistics were carried out using R 2.15 [28] with additional utility from the 'car', 'ggplot2' [29],'mediation' [30], and 'sandwich' [31] packages.

RESULTS

Study population

Persons with dementia were significantly older, had more severe disease (as measured by H&Y and UPDRSm), and longer disease duration (Table 1). There were no significant differences in mean education or vitamin D concentrations between the groups. There was a significant association between vitamin D and disease severity, as measured by both H&Y and UPDRSm ($r = 0.191$, $p = 0.0013$ and $r = 0.242$, $p = 0.0025$).

Cognitive measures

Significant differences between demented and nondemented subjects were found for all evaluated neuropsychiatric tests (Table 2). Prior to multivariate model adjustment, initial analysis revealed significant simple univariate correlations between vitamin D and vegetable fluency for the entire Udall cohort (Pearson's $r = 0.191$, $p = 0.013$) as well as the nondemented subset (Pearson's $r = 0.242$, $p = 0.0025$) but not for the demented subjects (Pearson's $r = -0.0603$, $p = 0.81$) (Table 3). With respect to the multivariate models, analysis of the neuropsychiatric tests revealed significant associations between vitamin D concentrations and fluency for naming vegetables ($t = 4.04$, $p < 0.001$), naming animals ($t = 2.53$, $p = 0.028$), immediate recall in HVLT ($t = 2.89$, $p = 0.015$) and delayed recall in HVLT ($t = 3.18$, $p = 0.012$) when looking at all participants (Table 4). In the non-demented sub-set, similar associations were found for naming vegetables ($t = 4.31$, $p < 0.001$), immediate HVLT recall ($t = 3.04$, $p = 0.0083$) and delayed HVLT recall ($t = 3.03$, $p = 0.0083$) although only a non-significant trend was observed for animal fluency ($t = 2.11$, $p = 0.086$) (Table 4). In the demented sub-set no significant associations were seen between cognitive testing and vitamin D. These associations were corrected for age, disease duration, and disease severity (using H&Y) and accounted for outlier removal for the multivariate models. Corresponding patterns of significance for the simple correlations were also observed for verbal fluency and memory after multivariate model adjustment (Fig. 1).

Mood measures

Prior to multivariate regression, vitamin D concentrations were significantly correlated with GDS in the non-demented subset (Pearson's $r = -0.193$, $p = 0.014$) and showed a non-significant trend in the entire cohort ($r = -0.150$, $p = 0.053$) (Table 3). These associaons were even more pronounced after accounting for the described covariates, significant for the entire cohort ($t = -2.83$, $p = 0.015$) as well as the non-demented subset ($t = -3.08$, $p = 0.0083$) (Table 4, Fig. 2).

Mediation analysis

Because of the known relationship between mood and cognition a mediation analysis was performed. In all cases, causal effects of mood underlying the relationship between vitamin D with verbal fluency and verbal recall were found to be nonsignificant. For the entire cohort, the direct effect between vitamin D and cognitive ability was observed to be significant (vegetable fluency: $\beta = 0.0456$, $p < 0.01$; animal fluency: $\beta = 0.0407$, $p = 0.02$; immediate HVLT: $\beta = 0.0643$, $p < 0.01$; delayed HVLT: $\beta = 0.0422$, $p < 0.01$) while mediation due to GDS score was not (vegetable fluency: $\beta = 0.00786$, $p = 0.14$; animal fluency: $\beta = 0.00649$, $p = 0.17$; immediate HVLT: $\beta = 0.0131$, $p = 0.12$; delayed HVLT: $\beta = 0.00592$, $p = 0.14$). This pattern held true for the three significant cognitive assessments in the non-demented cohort as well with significant direct effects due to vitamin D3 (vegetable fluency: $\beta = 0.0695$, $p < 0.01$; immediate HVLT: $\beta = 0.0602$, $p < 0.01$; delayed HVLT: $\beta = 0.0437$, $p < 0.01$) being observed but with non-significant mediation by GDS (vegetable fluency: $\beta = 0.00536$, $p = 0.18$; immediate HVLT: $\beta = 0.00764$, $p = 0.18$; delayed HVLT: $\beta = 0.00240$, $p = 0.37$).

DISCUSSION

Our data show that vitamin D concentrations relate to multiple measures of PD disease severity. Vitamin D concentrations also relate to multiple measures of neuropsychiatric function; specifically depression, verbal fluency, and verbal memory in persons without dementia.

Vitamin D concentration correlated with PD symptom severity, as measured by both H&Y and UPDRSm. We and others have found similar relationships in other studies [32, 33]. Prior studies have shown lower vitamin D concentrations in persons with later stage PD and in PD versus Alzheimer's patients and controls [34, 35]. It is possible that this is an example of reverse causation. Persons with more severe PD are less ambulatory, get less sun exposure, and subsequently have lower vitamin D. It is also possible that vitamin D has an effect on PD symptoms. The high density of the final converting enzyme and receptors for vitamin D in the substantia nigra make this an interesting question [7].

Because of the relationship of vitamin D and disease severity we corrected for this when looking at the associations between cognitive performance and vitamin D. Again reverse causation is possible. Persons with worse cognitive function may be more apt to forget to take vitamin D supplements. It is also possible that the worse cognitive performance is secondary to vitamin D having effects on mood. Depression is known to worsen cognitive performance. To examine this we performed a mediation analysis. This showed that vitamin D had a direct effect on the cognitive measures but there was no significant mediation effect of depression.

There are a number of hypotheses as to how vitamin D could influence cognitive function. It could be through established effects of vitamin D on the central nervous system via up regulation of neurotrophic factors, stabilization of mitochondrial function, or immunoregulation via antioxidant and anti-ischemic effects [36–38]. Vitamin D may also play a role in regulation of acetylcholine and clearing of amyloid beta peptide (the pathology seen in Alzheimer's disease) [39, 40].

There are a number of limitations to the study. Causation cannot be inferred using cross sectional data alone. In addition with the available data we are not able to determine clinical significance of the relationship between vitamin D and neuropsychiatric measures. The vitamin D levels were not significantly different between the non-demented and demented subjects (36.2 and 32.9 ng/ml $p = 0.16$) which would seem to suggest a limited effect of

vitamin D on cognition. Also we examined many cognitive measures that did not appear related to vitamin D concentrations. Another limitation of this study is that we did not collect explicit information on vitamin D supplementation. As this was an add-on study subjects were not asked about supplement use.

The fact that the relationship between vitamin D concentration and cognitive performance seemed more robust in the non-demented subset of the cohort suggests that earlier intervention studies before dementia is present may be more effective. Mild cognitive impairment (MCI) appears fairly common in PD, with a review reporting a prevalence of 26.7% [41]. Rates of MCI as high as 14.8%, have been found even in newly diagnosed PD patients [42]. It also appears that MCI predicts the future development of dementia [41, 43]. A recent study found verbal memory to be particularly predictive of progression from MCI to dementia (they did not assess verbal fluency) [44]. It should be feasible and would be appropriate for future intervention studies with vitamin D to include participants who are not yet frankly demented. Many have suggested that this is when therapies have the most promise of being effective. Our data supports further study of vitamin D supplementation for possible benefits on both mood and cognitive function.

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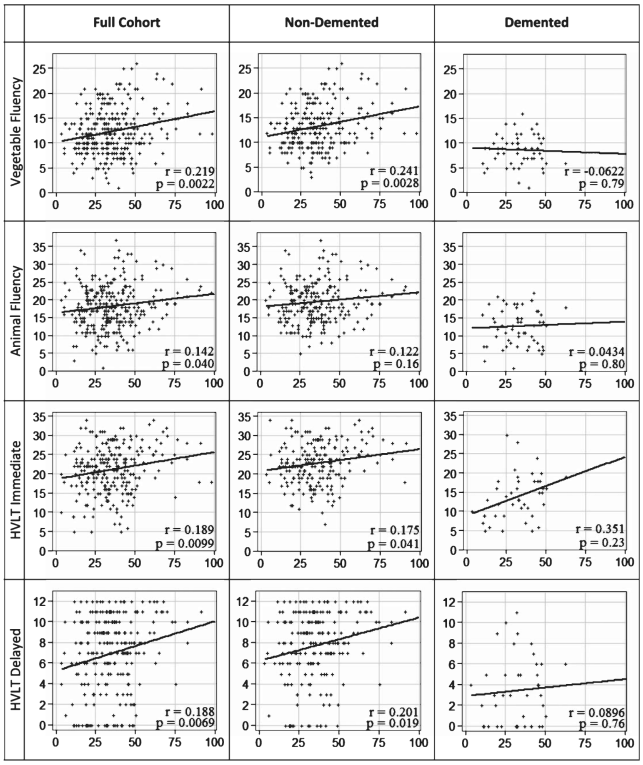

Figure 1.
Correlations of cognitive test results and vitamin D3 after multivariate multiple regression model adjustment.

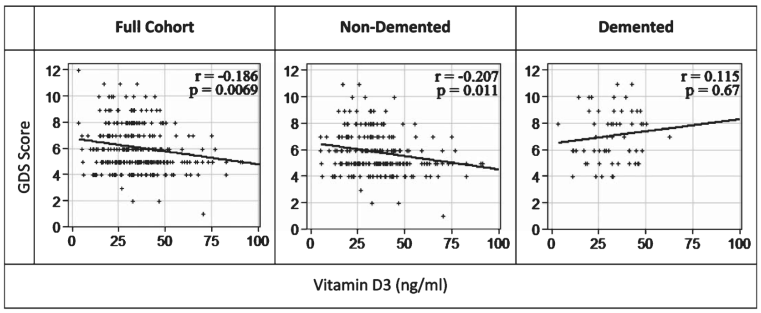

Figure 2.
Depression and vitamin D3.

Table 1

Cohort demographics

	Total (n=286)		Non-demented (n=225)		Demented (n=61)		Statistics
Gender	M	F	M	F	M	F	
	192	94	140	85	52	9	
Age(mean ± SD)	68.0±9.04		67.3±8.98		70.7±8.82		t = 2.65; p = 0.0095
PD duration (mean ± SD)	9.96±6.90		9.24±6.11		12.6±8.81		t = 2.81; p = 0.0063
UPDRSm (mean ± SD)	28.6±13.3		26.5±12.7		36.7±12.4		t = 5.57; p < 0.001
H&Y (mean ± SD)	2.56±0.749		2.48±0.698		2.88±0.845		t = 3.41; p = 0.0010
Years of education (mean ± SD)	16.0±2.76		16.1±2.69		15.6±2.97		t = 1.36; p = 0.17
Vitamin D3 (ng/ml) (mean ± SD)	35.5±17.0		36.2±17.3		32.9±15.6		t = 1.43; p = 0.16

Table 2

Descriptive statistics of neuropsychiatric tests

	Total (n = 286)	Non-demented (n = 225)	Demented (n=61)	Statistics
MMSE (mean ± SD)	27.5 (2.63)	28.2 (1.68)	24.8 (3.74)	t = 6.29; p < 0.001
MOCA (mean ± SD)	24.2 (3.52)	25.2 (2.73)	20.5 (3.92)	t = 8.38; p < 0.001
Mattis Scale (mean ± SD)	135 (8.73)	137 (5.60)	125 (12.1)	t = 6.26; p < 0.001
HVLT – Immediate (mean ± SD)	21.2 (6.43)	22.8 (5.34)	13.8 (5.89)	t = 9.21; p < 0.001
HVLT – Delayed (mean ± SD)	6.83 (3.80)	7.53 (3.55)	3.55 (3.17)	t = 7.23; p < 0.001
Vegetable Fluency (mean ± SD)	12.3 (4.63)	13.2 (4.44)	8.64 (3.50)	t = 8.19; p < 0.001
Animal Fluency (mean ± SD)	18.2 (6.35)	19.6 (5.79)	12.5 (5.20)	t = 8.97; p < 0.001
FAS Words Sum (mean ± SD)	38.4 (12.9)	41.2 (12.2)	27.1 (8.97)	t = 9.62; p < 0.001
Benton Line Orientation (mean ± SD)	11.8 (2.52)	12.1 (2.31)	10.3 (2.78)	t = 4.57; p < 0.001
Trails B Time (mean ± SD)	143 (87.9)	118 (71.9)	242 (76.1)	t =−11.0; p < 0.001
Digit-Symbol Score (mean ± SD)	37.6 (13.8)	40.1 (13.1)	26.3 (9.80)	t = 8.96; p < 0.001
GDS (mean ± SD)	6.07 (1.80)	5.83 (1.68)	7.00 (1.95)	t =−4.20; p < 0.001

Comparison between demented and non-demented with two-tailed t-test – Holm-Bonferroni corrected.

Table 3

Initial simple correlations of neuropsychiatric tests with vitamin D3 (Pearson's r; p-value)

	Total (n = 286)	Non-demented (n = 225)	Demented (n=61)
MMSE	0.0298; p = 0.71	−0.0128; p = 0.97	0.0862; p = 0.81
MOCA	0.0531; p = 0.49	0.00802; p = 0.97	0.173; p = 0.81
Mattis Scale	0.118; p = 0.25	0.0662; p = 0.69	0.173; p = 0.81
HVLT – Immediate	0.157; p = 0.053	0.132; p = 0.24	0.237; p = 0.81
HVLT – Delayed	0.0940; p = 0.31	0.0851; p = 0.55	0.0857; p = 0.81
Vegetable Fluency	0.191; p = 0.013	0.242; p = 0.0025	−0.0603; p = 0.81
Animal Fluency	0.0844; p = 0.31	0.108; p = 0.31	−0.0766; p = 0.81
FAS Words Sum	0.0591; p = 0.48	0.0552; p = 0.69	0.0339; p = 0.81
Benton Line Orientation	0.0220; p = 0.40	0.00262; p = 0.97	0.0493; p = 0.81
Trails B Time	−0.0237; p = 0.71	0.00516; p = 0.97	−0.0331; p = 0.81
Digit-Symbol Score	0.0727; p = 0.37	0.0428; p = 0.78	0.166; p = 0.81
GDS	−0.150; p = 0.053	−0.193; p = 0.021	0.0605; p = 0.81

Significance of direct correlations Holm-Bonferroni corrected.

Table 4

Associations of neuropsychiatric tests with Vitamin D3 – standardized coefficients from multivariate multiple regression corrected for age, gender and Parkinson's disease severity

	Entire cohort Vitamin D3	Non-demented Vitamin D3	Demented Vitamin D3
MMSE	β = 0.00924 t = 0.18, p = 0.86	β = 0.0108 t = 0.16,p = 0.94	β = −0.0781 =−0.64, p = 0.95
MOCA	β = 0.0528 t = 0.93, p = 0.53	β = 0.0390 t = 0.64, p = 0.70	β = 0.247 t = 1.40, p = 0.60
Mattis Scale	β = 0.0409 t = 1.04, p = 0.51	β = 0.0602 t = 1.00, p = 0.48	β = 0.123 t = 0.93, p = 0.86
HVLT – Immediate	β = 0.163 t = 2.89, p = 0.015	β = 0.196 t = 3.04, p = 0.0083	β = 0.328 t = 1.84, p = 0.60
HVLT – Delayed	β = 0.197 t = 3.13, p = 0.012	β= 0.208 t = 3.03, p = 0.0083	β = 0.0108 t = 0.082, p = 0.97
Vegetable Fluency	β = 0.233 t = 4.04, p < 0.001	β = 0.264 t = 4.31, p < 0.001	β =−0.0707 t =−0.53, p = 0.95
Animal Fluency	β = 0.144 t = 2.53, p = 0.028	β = 0.133 t = 2.11, p = 0.086	β = 0.0107 t = 0.058, p = 0.97
FAS Word Sum	β = 0.0463 t = 0.82, p = 0.55	β = 0.0652 t = 1.04, p = 0.48	β = 0.00503 t = 0.034, p = 0.97
Benton Line Orientation	β = 0.0333 t = 0.63, p = 0.63	β = 0.0199 t = 0.33, p = 0.89	β = 0.0573 t = 0.48, p = 0.95
Trails B Time	β =−0.0179 t =−0.34, p = 0.80	β =−0.00416 t =−0.072, p = 0.94	β = 0.0145 t = 0.086, p = 0.97
Digit Symbol Score	β = 0.0796 t = 1.55, p = 0.24	β = 0.0562 t = 1.05, p = 0.48	β = 0.229 t = 1.45, p = 0.60
GDS	β =−0.170 t =−2.83, p = 0.015	β =−0.205 t =−3.08, p = 0.0083	β = 0.229 t = 1.30, p = 0.60

Significance of multiple comparisons Holm-Bonferroni corrected.