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Caffeine and Progression of Parkinson Disease

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Caffeine and progression of Parkinson's disease: A deleterious interaction with creatine

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Abstract

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CONFLICT OF INTEREST

Other authors have no relevant conflicts of interest.

Objective—Increased caffeine intake is associated with a lower risk of Parkinson's disease (PD) and is neuroprotective in mouse models of PD. However, in a prior study, an exploratory analysis showed that, in patients taking creatine, caffeine intake was associated with a faster rate of progression. In the current study we investigated the association of caffeine with the rate of progression of PD and the interaction of this association with creatine intake.

Methods—Data were analyzed from a large Phase 3 placebo-controlled clinical study of creatine as a potentially disease-modifying agent in PD. Subjects were recruited for this study from 45 movement disorders centers across the United States and Canada. A total of 1,741 PD subjects participated in the primary clinical study, and caffeine intake data were available for 1,549 of these subjects. The association of caffeine intake with rate of progression of PD as measured by the change in the total Unified Parkinson Disease Rating Scale (UPDRS) score, and the interaction of this association with creatine intake, were assessed.

Results—Caffeine intake was not associated with the rate of progression of PD in the main analysis, but higher caffeine intake was associated with significantly faster progression among subjects taking creatine.

Conclusions—This is the largest and longest study conducted to date that addresses the association of caffeine with the rate of progression of PD. These data indicate a potentially deleterious interaction between caffeine and creatine with respect to the rate of progression of PD.

INTRODUCTION

Caffeine has a dose-depended inverse association with the risk of developing Parkinson's disease (PD)(1, 2)Caffeine is an antagonist at adenosine A2a receptors, although a recent study suggested that it may act as an A2a inverse agonist(3). Both caffeine and other more specific A2a receptor antagonists are neuroprotective in toxin-induced PD animal models(4). Furthermore, mice lacking the A2a receptor are protected against dopaminergic neurodegeneration induced by mutant α-synuclein(5). These data have led to the hypothesis that caffeine may have a neuroprotective effect in PD. As a preliminary test of this hypothesis, we previously analyzed data from 2 Phase 2 futility-design clinical studies of potential disease-modifying therapies in PD. Arms in the studies included creatine, minocycline and placebo in one study (FS1)(6); and coenzyme Q10, GPI-1485 (an immunophilin ligand) and placebo in the other(FS2)(7). A caffeine intake questionnaire was completed by participating subjects. Unexpectedly, among subjects randomized to creatine, increasing levels of caffeine intake were associated with significantly faster progression of PD as measured by the change in the total UPDRS score, whereas there was no consistent association of caffeine with progression in other treatment groups(8). We sought to replicate and extend this surprising but potentially important observation by analyzing the association of caffeine intake with the rate of progression of PD as a substudy of a large multicenter double-blind, placebo-controlled Phase 3 clinical study of creatine as a potentially disease-modifying therapy in PD, the "Large Long Term Study" (LS1)(9).

METHODS

Study subjects and the LS1 study

A total of 1,741 early PD subjects (diagnosed within 5 years) already treated with dopaminergic therapy were enrolled in LS1 and randomized 1:1 to creatine 10 grams per day or placebo. Subjects were recruited from 45 sites in the US and Canada. All subjects were within 5 years from diagnosis and were receiving dopaminergic therapy (levodopa or a dopamine agonist) for at least 90 days but no more than 2 years at the time of recruitment into the study. This study was sponsored by the National Institute of Neurological Disorders and Stroke (NINDS). Details of the study design and characteristics of participants have been published elsewhere(9, 10). The goal was to follow all subjects for a minimum of 5 years; however, a preplanned interim analysis conducted when half of the subjects had reached the 5-year time point suggested that creatine was unlikely to meet the pre-specified threshold for significant slowing of clinical disease progression, and the study was terminated early. All study procedures were approved by institutional review boards at each participating site.

Caffeine questionnaire

A total of 1,549 subjects completed a caffeine intake questionnaire that had been used previously in the Futility Study (FS)1 study(8). This questionnaire focused primarily on intake of caffeinated beverages during the prior week. The majority of subjects who completed the questionnaire did so at the 18-month time point of the study. In this analysis we did not take into account those who did not complete a questionnaire, but data comparing characteristics of those who completed or did not complete the caffeine questionnaire are presented.

Statistical methods

The primary outcome measure was the total Unified Parkinson's Disease Rating Scale (UPDRS) score during all years of follow-up, with baseline UPDRS included as a covariate. For all analyses (baseline and follow-up) we defined "total UPDRS" as the sum of scores for a participant for UPDRS parts I-III. The UPDRS was selected *a priori* for this analysis as this measure was used in our prior study based on data from the FS1 and FS2 studies(8). We sought to determine if we could replicate the results of that prior study in the current analysis of data from the larger and longer duration LS1. The distribution of daily caffeine consumption was zero-inflated and highly skewed to the right. A log and square root transformation did not lead to normally distributed data due to the high percentage of zero values. Therefore, caffeine was analyzed as a categorical variable, with subjects split into high and low caffeine intake groups. The low caffeine group was defined as subjects with daily caffeine intake less than or equal to 300 mg. The high caffeine group had caffeine intakes greater than 300 mg per day. This cutoff of 300mg has been used in previous studies Ascherio, 2001 #645;Fernandez-Duenas, 2014 #3085;Ross, 2000 #644;Schwarzschild, 2003 #3082} of health-related impacts of caffeine consumption.

Baseline characteristics were compared for the low (N=1,288) and high (N=261) caffeine groups. P-values from Wilcoxon and Chi-square tests were obtained for continuous and binary variables respectively.

To assess the effect of caffeine while adjusting for other covariates and interactions, a mixed model was used with site as random effect. The response variable was the annual total UPDRS score from year 1 to 5. The mixed model used all available longitudinal annual measurements of UPDRS, assuming the correlation structure of multiple measurements within each individual to be Heterogeneous Auto Regression One (ARH1). The Auto Regression (AR1) structure assumes the correlation of yearly UPDRS is mainly related to measurements in neighboring years and the relationships decrease as the time between measurements increase. The heterogeneous structure relaxed the variance assumption for each measurement and allows a different variance at each time point.

Models were fit by SAS PROC MIXED using REML method. Fixed effect parameters were estimated for every model. REML in PROC MIXED accommodates data that are missing at random. Missing data in our sample were mostly due to loss of follow-up, drop-outs or deaths. Loss of follow-up here refers to loss due to early trial closure; drop-outs appeared to be unrelated to caffeine and thus were considered missing at random as well. Death could be considered missing at random only if the reason for death was not related to caffeine consumption. There was no association of caffeine intake with cardiac death in this data set, a cause of death that in theory might have been related to caffeine, so death also was considered missing at random.

We fit the basic model using caffeine category (high versus low) along with other variables of clinical interest, which included treatment group, age at enrollment, years since enrollment (year), baseline UPDRS score, and gender as main effects. Treatment by caffeine interaction, treatment by gender interaction, and year interactions with treatment, caffeine, age, gender and baseline UPDRS, as well as the three way interactions of treatment*caffeine*year, treatment*gender*year, caffeine*gender*year were tested for their significance by interaction plots and Wald Test p values. The final basic model included significant main effects at the 0.05 level and significant interactions at the 0.1 level.

Next we assessed the confounding and modifying effect of covariates that might associate with caffeine or disease progression. First, the pairwise correlation was computed between continuous variables. In order to avoid multi-colinearity, variables that were highly correlated were not both kept in the model. Each covariate was added to the basic model to test its influence on disease progression. Their interaction with caffeine also was tested by two-way and three-way interactions with time. Wald Test with p values less than 0.05 for main effects and 0.1 for interaction terms were used to select variables for the final model. Main effects remained in the model if any interactions including this main effect were significant. Final model diagnostics checked the normality of the residual plot and the pattern of residual versus predictors. If a significant interaction of treatment (creatine versus placebo) by caffeine group was detected, separate models for treatment groups were built to assess the effect of caffeine in the different groups.

RESULTS

Baseline characteristics of the 1,549 subjects who completed the caffeine questionnaire and for the 192 subjects who did not are shown in **Table 1**. Most baseline characteristics were not significantly different between these 2 groups. Subjects who did not provide caffeine intake data had significantly higher baseline Beck Depression Inventory (BDI) scores, UDPRS scores and levodopa dose equivalents, suggesting that depressive symptoms or more severe PD symptoms may have reduced the chances of completing the caffeine questionnaire.

The distribution of caffeine intake is shown in **Figure 1**. **Table 2** compares baseline characteristics for subjects in the high and low caffeine groups. Uric acid levels were compared due to the association of uric acid levels with rate of progression of PD(11), and to reports that high caffeine intake may be associated with lower uric acid levels(12). Median uric acid levels and median body mass index (BMI) were significantly higher in subjects in the high caffeine group, whereas days since diagnosis at the time of study entry was lower in the high caffeine group. A significantly lower percentage of female subjects was present in the high versus low caffeine group.

In the final model, there was a significant 3-way interaction between treatment group (creatine versus placebo), caffeine category (high versus low) and years since enrollment in assessing the association with total UPDRS score (i.e. rate of progression). Therefore, the placebo and creatine groups were analyzed separately. For the placebo group, caffeine and rate of progression did not interact. In contrast, there was a significant interaction between caffeine and rate of progression for the creatine group, with high caffeine intake being associated with more rapid progression (**Figure 2** and **Table 3**; $p = 0.002$). Uric acid was not statistically significant in either model (p-values >0.1), and so was not included in the model based on our model selection criteria.

The lack of an interaction between caffeine and rate of progression in the placebo group is consistent with a similar analysis in a previously published study(8). However, it remains possible that even modest levels of caffeine below the 300mg cutoff used for our primary analysis might be associated with slowing of clinical progression of PD, which would limit our ability to detect an association of caffeine with rate of progression using the 300mg threshold. To address this possibility, we conducted an additional post-hoc analysis of caffeine and rate of progression comparing subjects with very low caffeine intake (<25mg/day; n=662) to those in the high caffeine group (>300mg/day; n=261), and again there was a lack of a significant interaction in the placebo group.

An interesting possibility raised by these results is that the association of high caffeine intake with a faster rate of progression among subjects taking creatine may have masked a protective effect of creatine among subjects with low levels of caffeine intake. However, subgroup analyses restricted to subjects in the low caffeine group (<300mg/day; n=1,288) or the very low caffeine group (<25mg/day; n=662) revealed no significant associations of treatment (creatine versus placebo) and rate of progression of PD.

DISCUSSION

Epidemiological data indicate a dose-dependent association of caffeine intake with the risk of PD(1, 2). Furthermore, caffeine is neuroprotective in animal models of PD(4), raising the possibility that caffeine also may have neuroprotective effects in PD patients. Therefore, we predicted that high caffeine intake would be associated with slower progression of PD. Contrary to this prediction, we found that among patients randomized to take creatine, higher caffeine intake was associated with a significantly faster rate of progression of PD, whereas there was no significant association detected for caffeine with the rate of progression among placebo subjects.

In a prior study of 2 smaller clinical cohorts, we similarly found no association of caffeine intake with the rate of progression of PD(8) over 12 months. This prior study also unexpectedly identified a significant association of caffeine with a faster rate of progression among subjects taking creatine, but this finding was not considered to be definitive due to the small number of subjects in that study (n = 64 subjects on creatine), the lack of an *a priori* prediction of this result, and a result of borderline significance. In contrast, the current study included clinical progression data for up to 5 years from 1,549 subjects. Furthermore, based on the results of the prior study, for the current study we specifically hypothesized a priori that higher caffeine intake would be associated with faster progression among subjects taking creatine. Indeed, we confirmed this result ($p = 0.002$), suggesting a deleterious interaction between caffeine and creatine with respect to the rate of clinical progression of PD. Although data on the frequency of combined use of creatine and caffeine in the general population are not available, caffeine use is common, with 17% of PD subjects in the LS1 study having intakes greater than 300mg/day. Creatine supplements also are common among certain populations, with one study suggesting that 50% of high school senior football players using creatine supplements(13). However, the prevalence of creatine use in the general PD population is unknown. The current study was restricted to PD patients and so it remains unknown if there may be a deleterious interaction between creatine and caffeine use in people who do not have PD or in a younger population.

The LS1 trial of creatine ended early for futility based on a pre-planned interim analysis. Our observation of a faster rate of progression among subjects with high levels of caffeine intake raises the interesting possibility that creatine may actually have had a beneficial effect among subjects with lower levels of caffeine intake, but this effect was negated by the deleterious effect among subjects with high levels of caffeine intake. However, no significant association of creatine with rate of progression of PD even was detected when considering only those subjects in the low caffeine group (<300mg/day) or only those subjects with very low caffeine intake (<25mg/day).

Recent data have suggested that caffeine may have a symptomatic benefit in PD(14). We observed a similar mean levodopa equivalent dose at baseline among subjects in the low and high caffeine groups, and a nonsignificant trend towards lower baseline UPDRS scores in the high caffeine group. However, because this study was not randomized with respect to caffeine intake, the lower baseline UPDRS scores do not necessarily imply a symptomatic benefit from caffeine. In any case, a symptomatic effect of caffeine on PD symptoms should

not complicate our analysis of the association of caffeine intake with progression of PD unless either the level of caffeine intake changes during the study, or if the magnitude of the symptomatic benefit of caffeine changes as the disease progresses.

The potential mechanism by which caffeine and creatine may negatively interact with respect to the rate of progression of PD is not addressed in the current study. A prior study suggested that caffeine completely negates the effects of creatine on muscle contraction(15, 16), potentially by counteracting the creatine associated facilitation of calcium uptake by the sarcoplasmic reticulum(16). It is interesting to note that high caffeine intake was associated with a mild but significant increase in uric acid levels (Table 2). This contrasts with prior reports of an association of caffeine with lower serum uric acid levels(17), and suggests that the relationship between caffeine intake and uric acid level may be different in PD patients compared to the general population. Uric acid is an antioxidant and high uric acid levels have been associated with a lower risk of PD and with a slower rate of progression of PD(18). However, despite the higher uric acid levels in the high caffeine group, we did not detect an association of high caffeine use with a slower rate of progression of PD.

This study has several strengths, including a large population of PD patients with detailed clinical assessments by movement disorders specialists over several years, as well as availability of data on caffeine intake for a majority of the subjects. There also are limitations. Caffeine data were collected at only one time point during the study, and this was 18 months after baseline. Therefore, our analyses could not account for potential changes in levels of caffeine intake over the course of the study. In our previously published study a repeat caffeine questionnaire was administered after 1 year, and this demonstrated that the level of caffeine intake was relatively stable (changed by less than 25%) in ~90% of subjects(8). However, the percentage of subjects with changes in caffeine intake likely is greater in the current study due to its longer duration. Not all participants provided caffeine data, although baseline differences between those who provided data and those who did not were minimal. The most important drawback is that subjects were not randomized or blinded with respect to caffeine intake. It is possible that other factors that are associated with caffeine use could influence these results. Relating to this point, data on smoking were not collected for the LS1 subjects. There is an association with caffeine and tobacco use(19). This raises the possibility that the associations with caffeine reported in this study may reflect an influence of tobacco use. However, the current results replicate our prior report that caffeine use is inversely associated with rate of clinical progression of PD in subjects taking creatine, and results in the prior study remained significant after adjusting for smoking(8). Similarly, in a study by Hamza et al identifying GRIN2A genotype as a modifier of the influence of caffeine on the risk of PD, the results were similar before and after adjusting for smoking(4). Furthermore, the frequency of smoking is low in PD patients(19), and so this issue is likely to be relevant to only a small percentage of LS1 subjects. A case control study of over 500 PD patients and a similar number of controls at movement disorders centers in the US revealed that only 3.6% of PD subjects smoked cigarettes and also had significant caffeine intake(20)(Tanner et al., unpublished data).

An additional possible limitation is the retrospective self-reported nature of the caffeine questionnaire, although studies on caffeine intake quantification have documented the validity of self-report methods(21).

In conclusion, these data show no association of caffeine with the rate of clinical progression of PD except in the group of participants taking creatine where progression was increased. This study was not randomized or blinded with respect to caffeine intake. For this reason, and based on the strength of epidemiological and preclinical data suggesting that caffeine may have neuroprotective effects in PD, further study of the potential neuroprotective effects of caffeine and other A2a receptor antagonists remains warranted. Given the lack of any benefits of creatine for PD patients in the LS1 study, as well as the possibility of a deleterious effect when combined with caffeine, it remains prudent to recommend against creatine supplementation for PD patients.

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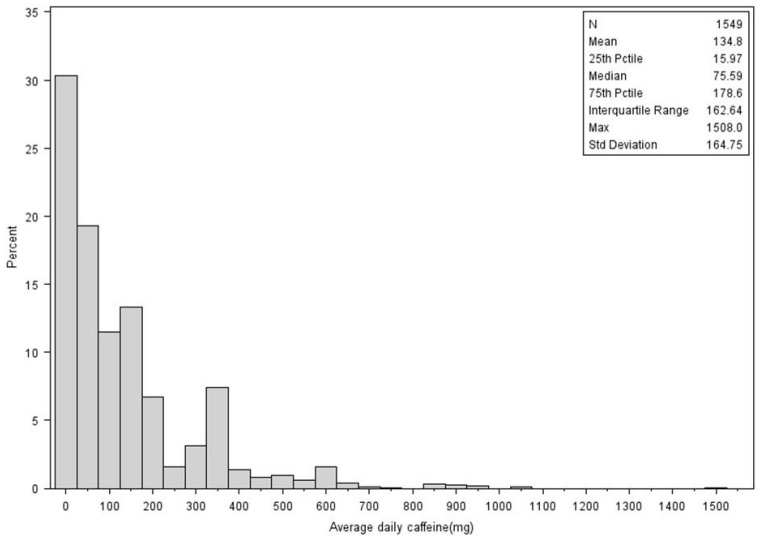

Figure 1. Distribution of daily caffeine intake

Distribution of daily caffeine intake among the 1,549 subjects for whom caffeine intake data were available. The mean intake was 134.8mg per day

Figure: 2A: The association of caffeine category with the rate of UPDRS total score change per year in the creatine group

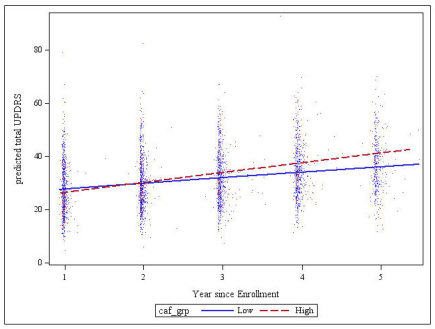

Figure 2B: Interaction Plot of caffeine by treatment on the total UPDRS score

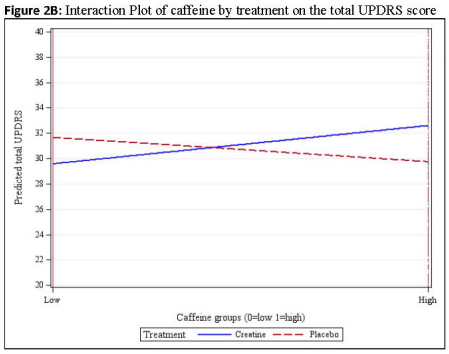

Figure 2. Caffeine and total UPDRS

2a) Loess plot for total UPDRS over year by caffeine categories. The y axis used the fitted value of total UPDRS from the creatine subgroup model (Table 3). The smoothing parameters are automatically selected by SAS PROC SGPLOT.

2b) Interaction plot of treatment by caffeine categories over total UPDRS. The y axis is the fitted UPDRS from the final model for the whole population. Smoothing parameter is 0.3 in SAS PROC SGPLOT.

Table1

Baseline characteristics of those who completed the caffeine questionnaire to those who did not.

		Caffeine data available N=1549	Caffeine data NOT available N=192	p-value[1]
Levodopa Equiv.	Median	300.0	389.5	<0.001**
Dose at Baseline	SD	242.31	255.49	
	IQ range*	225.0	275.0	
Beck Depression	Median	6.0	6.5	<0.007**
Index	SD	5.40	6.49	
	IQ range	6.0	9.0	
Uric Acid	Median	5.0	5.1	0.51
	SD	1.34	1.38	
	IQ range	1.8	1.6	
Body Mass Index	Median	27.0	27.7	0.12
	SD	7.07	5.64	
	IQ range	5.9	5.5	
Age at Enrollment	Median	62.0	64.0	0.15
	SD	9.39	11.42	
	IQ range	12.0	14.0	
Days since Diagnosis	Median	483.0	470.5	0.78
	SD	401.0	347.36	
	IQ range	496.0	482.5	
UPDRS Baseline	Median	24.0	29.0	<0.0001***
	SD	11.08	13.10	
	IQ range	15.0	17.5	
Female	Freq	553	65	0.61
	%	35.70	33.85	
Treatment(Creatine)	Freq	776	98	0.80
	%	50.10	51.04	

[1] Continuous variables are tested using Wilcoxon Two-Sample Test; Binary variables are tested using Chi-square test.

* IQ range is interquartile range.

Table 2

Baseline characteristics of subjects in the low (≤300mg) and high (>300mg) caffeine intake groups

		Low Caffeine N=1288	High Caffeine N=261	p-value[2]
Levodopa Equiv. Dose at Baseline	Median	300.0	300.0	0.38
	SD	236.73	267.74	
	IQ range*	225	300.0	
Beck Depression Index	Median	6.0	5.0	0.12
	SD	5.45	5.11	
	IQ range	6.0	6.0	
Uric Acid	Median	5.0	5.3	0.04**
	SD	1.34	1.34	
	IQ range	1.9	1.8	
Body Mass Index	Median	26.7	27.8	<0.0001***
	SD	7.37	5.31	
	IQ range	5.9	5.3	
Age at Enrollment	Median	62.0	61.0	0.23
	SD	9.42	9.24	
	IQ range	13.0	13.0	
Days since Diagnosis	Median	493.0	412.0	0.003**
	SD	404.42	379.06	
	IQ range	492	480	
UPDRS Baseline	Median	25.0	22.5	<0.07*
	SD	11.17	10.55	
	IQ range	15.0	15.0	
Female	Freq	490	63	<0.0001***
	%	38.04	24.14	
Treatment(Creatine)	Freq	647	129	0.81
	%	50.23	49.43	

[2]Continuous variables are tested using Wilcoxon Two-Sample Test; Binary variables are tested using Chi-square test.

*IQ range is interquartile range.

Table 3

Final models for the subgroup of subjects randomized to creatine (N=765) and to placebo (N=770)

Effect for Creatine Sub-Group	Estimate	Standard Error	DF	t Value	Pr > |t|
Intercept	3.54	2.84	49	1.25	0.22
Baseline UPDRS	0.76	0.03	3028	24.91	<.0001***
+Years since enrollment	----	----		----	----
+Caffeine category	----	----		----	----
Gender	−1.40	0.67	3028	−2.08	0.04**
Age	0.01	0.04	3028	0.24	0.814
Beck Depression Inventory (BDI)	0.24	0.06	3028	3.91	<.0001***
Years since enrollment*Age	0.07	0.02	3028	4.40	<.0001***
Years since enrollment*Caffeine category	1.29	0.42	3028	3.07	0.002**
Effect for Placebo Sub-Group					
Intercept	9.81	2.80	48	3.50	0.001
Baseline UPDRS	0.75	0.03	3067	25.58	<.0001***
+Years since enrollment	----	----	----	----	<.0001***
Caffeine Category	−0.21	0.73	3067	−0.29	0.77
Gender	−2.20	0.58	3067	−3.80	0.0001***
+Age	----	----	----	----	0.06*
Beck Depression Inventory (BDI)	0.2158	0.05522	3067	3.91	<.0001***
Years since enrollment*Age	0.1110	0.01615	3067	6.87	<.0001***

+Where there is an interaction the main effect is difficult to interpret and is not reported.