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APOE GENOTYPE INFLUENCES POSTPRANDIAL BLOOD PRESSURE AFTER HIGH FAT FEEDING IN OLDER ADULTS

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Abstract: *Objective:* Postprandial hypotension (PPH) is a common phenomenon among older adults. The degree to which individuals experience PPH is related to cerebrovascular risk factors and the presence of neurodegenerative diseases such as Alzheimer's disease (AD). Carrier status of the E4 allele of the apolipoprotein E (APOE) gene is a risk factor for AD and influences a variety of responses to metabolic and dietary interventions. However, it is unknown whether APOE genotype influences the risk of PPH and whether type of meal can mediate that response. *Design:* Acute meal study with a crossover design. *Participants:* 32 cognitively healthy older adults with (n=18) and without (n=14) E4+ carrier status. *Intervention:* As a part of an ongoing meal study we examined the postprandial blood pressure response after ingestion of a high carbohydrate (HCM) and high fat meal (HFM). *Measurements:* Blood pressure measurements were taken at 7 time points and change scores, area under the curve (AUC) scores were calculated. Data were analyzed by repeated measures ANOVA as well as Pearson correlation. *Results:* Both meals produced a sustained drop in systolic (SBP) and diastolic (DBP) blood pressure, with 37.5% of participants meeting criteria for PPH. Participants carrying the E4+ risk gene experienced a larger decrease in SBP than E4- participants, and this was significantly different after the HFM (E4+ AUC = -30.8 ± 7.6, E4- AUC = -0.2 ± 8.7, p=0.015). Increasing age was associated with a larger drop in postprandial blood pressure but only for the E4+ group after the HFM (p=0.002). *Conclusions:* These data suggest that E4+ individuals experience a greater postprandial blood pressure response particularly following high fat feeding, and this effect becomes more pronounced with age. The prevalence of PPH may play a role in the development of AD and may be mediated by diet.

Key words: Postprandial blood pressure, carbohydrates, fats, diet, Alzheimer's disease, apolipoprotein E (APOE).

Abbreviations: AD: Alzheimer's disease; APOE: apolipoprotein E (gene); apoE: apolipoprotein E (protein); AUC: area under the curve; BMI: body mass index; DBP: diastolic blood pressure; HCM: high carbohydrate meal; HFM: high fat meal; HR: heart rate; HTN: hypertension; PPH: postprandial hypotension; SBP: systolic blood pressure;

Introduction

Postprandial hypotension (PPH) is clinically defined as a decrease in systolic blood pressure (SBP) of 20 mmHg or more within 2 hours after eating (1). It has been well documented in older adults (2-6) and can be accompanied by falls and syncope (7). Individuals with neurological diseases are at greater risk of PPH, including Alzheimer's disease (AD), Parkinson's disease and diabetic neuropathy (4, 8-10). Other risk factors include both hypertension (HTN) and severe hypotension (10, 11). The connection between cerebrovascular disease on neuroimaging and clinical PPH suggest that disruption of normal cerebral autoregulation may play a role in PPH pathogenesis (1, 7, 10-13).

In addition to patient risk factors, meal type may influence PPH. The macronutrient content of meals can influence the degree of PPH, with meals rich in sugar or carbohydrate inducing significant PPH in older adults (3, 5, 10, 14). A growing body of literature suggests that the macronutrient component of diet has an effect on both short-term cognition as well as cognitive aging and development of AD (15, 16). Possession of the E4 allele of the apolipoprotein E gene (APOE4) is a risk factor for AD, compared to the E2 and E3 alleles (17). This risk factor directly influences cerebrovascular function and synergizes with other vascular risk factors such as HTN to modulate AD risk indirectly (18). We and others have shown that E4 status influences the connection between dietary risk factors and AD. For example, E4+ individuals respond differently to high fat feeding and an oral glucose drink compared to their E4- counterparts, suggesting that APOE genotype influences the relationship between diet and cognitive aging (19, 20).

Despite extensive research in PPH in older adults, it is unknown whether APOE genotype influences this phenomenon. We are conducting a meal intervention in older adults comparing cognitive and biomarker responses to high carbohydrate versus high fat feeding which includes several BP measures; therefore, we examined whether we could detect differences in PPH by macronutrient composition, and whether APOE genotype influences PPH.

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Methods

This research is a part of an ongoing study (CT# NCT03070535) designed to assess the cognitive and brain metabolic effects of high carbohydrate and high fat feeding in older adults at risk for AD. Older adults were recruited from the community, and inclusion criteria included normal cognition and age 55 or older. Exclusion criteria included diabetes, statin use, sex hormone use, known dementia, significant liver or kidney disease, and use of blood thinners. Participants were told about the goals of the study, methods, and risks and gave their written consent. The investigation was approved by the Institutional Review Board of the University of Washington. After consenting, participants underwent a screening visit consisting of vitals, a physical exam, memory screen, depression and anxiety screen, and a blood draw to detect exclusion criteria and to ascertain APOE genotype.

This study is single-blind and each participant served as their own control over two meal visits. After a 12-hour overnight fast, participants were served a single breakfast style meal (~700 kcal) in random order, either the high fat meal (HFM, 30% carbohydrate, 50% fat with half being saturated fat, 20% protein, glycemic index >70) or the high carbohydrate meal (HCM, 55% carbohydrate, 25% fat with one-fifth being saturated fat, 20% protein, glycemic index < 55). Participants were encouraged to try everything on their plate to ensure that the macronutrient ratio would remain relatively constant regardless of caloric intake. Participants were encouraged to eat at a regular pace (average time to finish meal 24 minutes) and were offered small salt and pepper packets with the HFM to season the hard-boiled egg component. Single measures of heart rate, blood pressure, and blood glucose were taken at 0 min, 15 min, 30 min, 60 min, 120 min, 180 min, and 240 min using a Welch Allyn machine cuff around the upper arm, ensuring proper cuff size. Participants were encouraged to sit or lie in bed for the duration of the study but were permitted to use the restroom and stretch. After the 180-min time point, participants completed an hour-long cognitive battery and cognitive exam. After the 240-min time point, participants underwent a lumbar puncture. Meal visits were spaced 3-5 weeks apart.

Pooled t tests and Chi square analyses were used to compare baseline demographics by group. Repeated measures ANOVAs were performed using SAS (University edition, 2018) to analyze the change in vitals over time. GraphPad Prism (Version 7.03) and the trapezoid rule was used to calculate AUC measures. Correlations were performed in SAS using the Pearson method.

Results

Baseline demographics

Table 1 shows the baseline information about the study participants, which was collected on a day before the two meal visits. Participants ranged from 55 to 84 years of age and included more women than men; however, the fraction did not significantly differ by E4 group (Chi square statistic p=0.67). The E4 groups did not differ by age or BMI. Eight individuals had hypertension (6 in E4+ group), either by self-report or having a BP >140/90 on screening visit, and 3 individuals were on medications for HTN. The E4+ group had a higher baseline DBP (p=0.0237). The racial and ethnic demographics of the participants reflected the demographics of the community.

Table 1
Baseline demographics, mean ± standard deviation

	All	E4-	E4+
n (# female)	32 (22)	14 (10)	18 (12)
Age (years)	64.8 ± 6.7	66.1 ± 6.4	63.7 ± 6.9
BMI (kg/m^2)	25.7 ± 5.0	24.9 ± 3.3	26.3 ± 6.0
# with HTN (# on med)	8 (3)	2 (1)	6 (2)
Baseline SBP	124.3 ± 14.4	120.6 ± 14.7	127.1 ± 13.9
Baseline DBP	75.6 ± 12.4	70.1 ± 9.6	79.9 ± 12.8*
Baseline HR	63.3 ± 8.8	63.4 ± 7.3	63.2 ± 10.0

*E4+ > E4- group, pooled t test p=0.0237

Figure 1
Temporal representation of a study visit

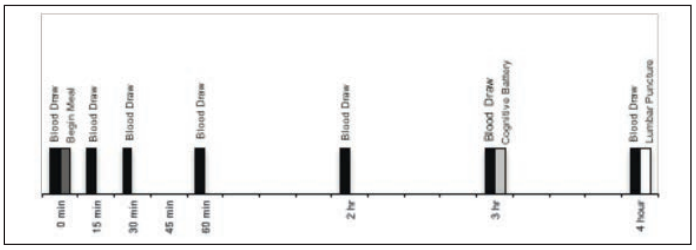


Table 2
Net AUC (mean ± standard error) of SBP change score by meal and E4 status, adjusted for age and baseline SBP

	HFM AUC	HCM AUC
E4-	-0.2 ± 8.7	-17.2 ± 12.3
E4+	-30.8 ± 7.6	-34.7 ± 10.8
P value by E4	0.015	0.306

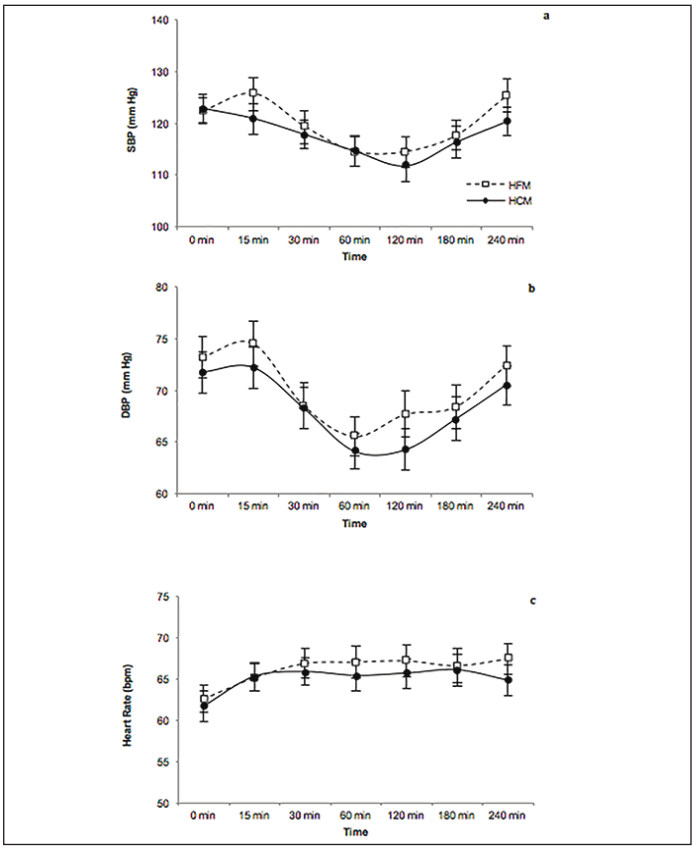
Post-prandial BP response

Figure 2 demonstrates the BP and HR pattern over the two meals for all participants. To investigate how time and type of meal affected post-prandial vitals, we performed ANOVA with the 7 time points as the repeated measure and meal (HFM vs HCM) as a class variable. Both SBP and DBP significantly changed after each meal (SBP*time F statistic = 17.34, p<0.0001, DBP*time F=23.49, p<0.0001). However, there was no difference between the meals for SBP (time*meal F=1.23, p=0.289) or DBP (time*meal F=0.53, p=0.786). The

drop in SBP occurred as early as 15 minutes for the HCM and at 30 minutes for the HFM. Heart rate increased on average of 4 beats per minute at the 15-minute time point (HR*time F=7.17, p<0.0001), but no meal-specific difference was noted (time*meal F=0.55, p=0.77). Both age and baseline systolic BP were found to be significant covariates in the ANOVA model and were included in all further analyses.

Figure 2

Time course of SBP (a), DBP (b), HR (c) following the HFM (dashed line) and HCM (solid line). For all graphs, the time effect was significant (p<0.0001) but did not differ by meal



Next the change scores (Δ in BP from Time 0) were calculated for SBP and DBP as per previous studies on PPH (3-6, 14). A higher percentage of E4+ participants met clinical criteria for PPH, defined as a drop in SBP by at least 20 points, regardless of starting value, within 2 hours of eating (1). In the E4- group, 1 participant met criteria after HFM and 3 different participants met criteria after HCM, for a total of 4 (28.6%). For the E4+ group, 5 met criteria after HFM and an additional 3 after HCM for a total of 8 (44.4%). Overall in this group of healthy older adults, 37.5% met criteria for clinical PPH. No PPH symptoms were reported; however, participants were encouraged to stay resting in bed throughout the study day. Next, we performed ANOVA using the 6 change scores as the repeated measure, E4 and type of meal as class variables, and age and baseline SBP as covariates. In this model, the E4 effect on SBP change score was significant (F=5.34, p=0.0244). We then analyzed data from each meal separately and for the HFM (Figure 3a), the E4 effect was significant (F=5.24, p=0.0299). E4+ participants had noticeably larger decreases in SBP starting around 60 minutes post meal and required 1 hour longer to return to baseline than the E4- group. For the HCM (Figure 3b), the E4 effect was not significant (F=1.47, p=0.2354), but the graphical pattern showed that E4+ participants had lower drops in SBP starting at 15 minutes and this group's SBP did not return to baseline whereas the E4- group returned to baseline after 240 minutes. Even though E4 carriers have a lower starting DBP (Table 1), we did not find any differences in post-prandial DBP change score by E4. Also, no significant effect of gender, or gender*E4 interaction, was found for the change scores (data not shown).

We next calculated the area between the curve and baseline (area under the curve, AUC) using GraphPad Prism software (Table 2). Similar to the repeated measures analyses, the AUC scores were larger for the E4+ group; however, this was only significant for the HFM. These AUC scores numerically demonstrate the visual pattern seen in Figure 3a: the average SBP change score AUC is near zero for the E4- group over 4 hours whereas the average AUC is -30.8 for the E4+ group.

There are 3 alleles for APOE and while possession of an E4 allele increases the risk of Alzheimer's, the E2 allele is protective, compared to the more common E3 allele (17). To examine whether the E2 allele influences this PPH response, we next analyzed the AUC data by 4 groups: the E2 group (combining the 22 and 23 genotypes), the E33 group, the E4 group (combining the 34 and 44 genotypes) and finally the E24 group. This stratification has been described in other studies as a way to examine the opposing effects of E2 and E4 given the rarity of homozygous 22 and 44 genotypes (21). For the HCM, the presence of an E2 allele didn't influence the pattern seen for E4- vs E4+ groups (Table 3). For the HFM we noted an interesting trend whereby the E2 group showed a net positive AUC compared to all other groups, but the E24 group unexpectedly showed the largest decrease in SBP AUC.

Table 3

Net AUC (mean ± standard error) of SBP change score by meal and APOE genotype group, adjusted for age and baseline SBP

	N	HFM AUC*	HCM AUC
E2 group (E22+E23)	5	21.8 ± 14.2	-13.6 ± 21.9
E33 group	9	-13.4 ± 10.7	-19.4 ± 16.5
E4 group (E34+E44)	14	-25.8 ± 8.4	-33.5 ± 12.9
E24 group	4	-46 ± 15.7	-38.5 ± 24.1

*Group 1 v 3, 1 v 4, p<0.05 (Least squares mean comparisons)

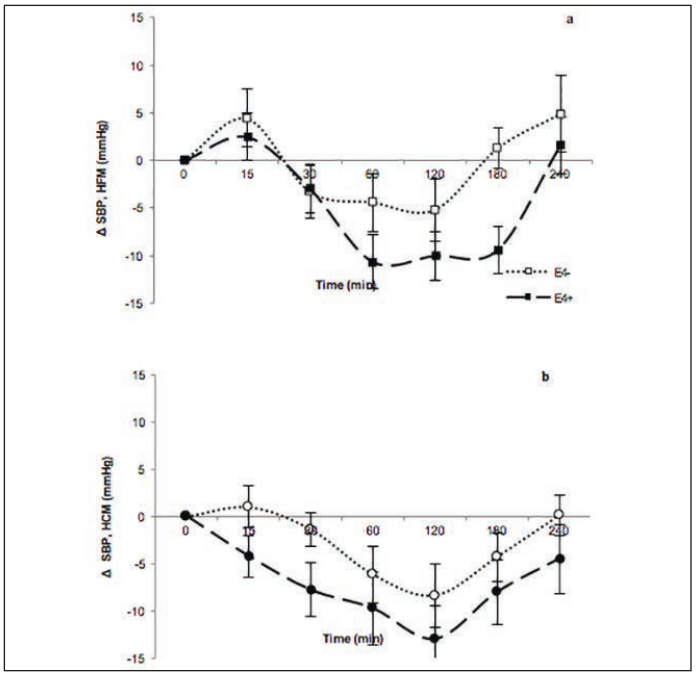
Age and BP

To explore the interaction of age and E4 status, we examined whether E4 status influenced the correlation between age and PPH AUC (Table 4). We found that age negatively correlated with the net AUC for SBP change score for the E4+ group for the HFM. For the HCM, there was a trend for a positive correlation for the E4- group and a negative correlation for the E4+ group.

Table 4
Correlation matrix of net AUC of SBP change score versus age: Pearson correlation coefficient (p value)

	HFM AUC vs age	HCM AUC vs age
E4- (n=14)	0.211 (0.469)	0.473 (0.088)
E4+ (n=18)	-0.678 (0.002)	-0.408 (0.093)

Figure 3
SBP change scores from time zero for the HFM (a) and HCM (b) for E4- (dotted line) and E4+ (dashed line). Time points were significant at 60 and 180 minutes for (a) after controlling for age and baseline SBP



Discussion

We were able to confirm with pilot data from this acute meal study that older adults demonstrate post prandial drops in blood pressure, and 37.5% of them met criteria for PPH during at least one meal. In this study, we did not identify a different pattern comparing high fat with high carbohydrate feeding. Notably we found that E4+ status significantly influenced the pattern of PPH, with any E4 allele being associated with a more significant BP drop, particularly after the high fat meal. Finally, in this group E4+ status tended to influence the relationship between age and PPH.

Meal macronutrients and PPH

We did not find a statistically significant difference between the meals for the pattern of PPH, but we did note a trend toward an increased systolic BP at 15 minutes after HFM compared to HCM, which could reflect the meal itself or the added salt participants could add to one of the meal components. Some research groups have found a more pronounced BP drop after high carbohydrate compared to high fat feeding, (1, 3, 5, 6, 10, 13, 14) and another study showed a sustained BP increase after high fat feeding (3, 6). However, one large study on a Mexican population found no correlation between macronutrient composition and PPH (4). One study found that warmer meals resulted in larger decreases in post-prandial blood pressure (22). This could have influenced the results of our study as the HCM contained a unique warmed element. Mechanisms for the earlier and more pronounced PPH after high carbohydrate feeding are not completely understood; some speculate it is due to increased amounts of insulin which can have a vasodepressor effect (1). Future studies in this area include measures of peripheral insulin and glucose, and determination of whether insulin changes correlate with PPH seen in this population. Of note, the uptrend in SBP at 3 and 4 hours after feeding in this population may also reflect stress levels of participants who are about to undergo cognitive testing and lumbar puncture, respectively. However, we did not notice a corresponding increase in heart rate at these time points, making this less likely to be a driver of their BP change.

APOE effects on PPH

We have previously shown that E4+ individuals demonstrate different metabolic and cognitive responses to macronutrients including high fat and high glucose meals, but this may be the first study to explore the relationship between APOE genotype and PPH in older adults (19, 20). We found that E4+ participants experienced a more substantial decrease in SBP and higher incidence of PPH following both meals. The effect was most apparent at the 3-hour mark for the HFM. We also found that in this group, any E4+ status was associated with the PPH finding. This was true for individuals with the E24 genotype, even though E2 carriers otherwise had a blunted PPH response. Individuals with an E2 allele (who do not carry an E4 allele) are at lower risk of developing AD (17). Thus, it follows that these individuals who are E24 may exhibit different postprandial vascular responses than those who are E33 homozygotes, or those carrying an E4 but not an E2 allele.

The purported mechanisms for PPH in older adults include several factors from the initial absorption of macronutrients to cerebral regulation of the sympathetic nervous system (reviewed in (1, 23)). Which of these factors account for the E4 effect on PPH, particularly seen for the HFM, are

unknown. APOE genotype may influence fat absorption, at least in children (24, 25), but this has not been thoroughly studied in older adults. Other potential peripheral mechanisms for PPH include differences in gastric emptying, mesenteric vasodilation, hormone secretion and sympathetic activation of cardiac tissue, vessels and baroreceptors. In the periphery, the apoE protein is involved in lipid absorption and transport (26) and could affect postprandial BP by influencing the absorption and subsequent metabolism of ingested lipids, or subsequent hormone secretion.

Cerebral autoregulation includes several mechanisms by which the brain can maintain constant blood flow over a wide blood pressure range. Both age and extremes of blood pressure tend to perturb this system and can lead to chronic damage, including white matter lesions (27). How PPH fits into this paradigm is unknown. Since E4+ status is known to influence several aspects of the cerebrovascular system, it is possible that higher PPH in this group is mediated by cerebral mechanisms. Altered cerebral blood flow is seen in E4 carriers as early as age 25 and becomes more pronounced in midlife (18). The apoE protein is abundant in vascular basement membranes, (28) and E4+ adults have heavier amyloid buildup in cerebral vessels which causes cerebral amyloid angiopathy (29). The brain controls blood pressure via communication between baroceptors and the medulla oblongata, thus E4+ status could affect blood pressure via amyloid disruption in the brain or abnormal amyloid in vessels leading to the brain. In addition, E4+ individuals have other defects within the blood brain barrier (BBB) which may influence the transport of lipids and hormones into the brain (30). One's E4+ status may affect the ability of certain molecules to pass the BBB, which may be further modulated by diet. It is known that E4+ status interacts with HTN to increase the rate of dementia and cognitive decline in older adults (18). In this study, the E4 findings were present even after controlling for baseline BP; however, this group was relatively free of both HTN and medication use for HTN. Therefore, this phenomenon needs to be studied in a larger population with respect to both E4+ status and concomitant HTN.

Interaction of age and APOE status

Carriage of the E4 allele is the strongest risk genetic factor for sporadic AD (17). Age has been positively correlated with incidence of PPH (12). We were able to demonstrate a correlation between age and PPH, but this relationship was only seen in the E4+ group. Given that these findings were detected in individuals who do not have cognitive impairment, this E4+ associated PPH may be clinically relevant to the pathophysiology of AD. Specifically, postprandial BP regulation could be one pathway through which dietary factors influence AD risk. Alternatively, identifying PPH could be included with other methods of early detection for identifying at risk individuals. Some view E4 as an accelerated aging phenotype, as those who are E4+ develop AD sooner than those who are E4-. This could be an alternative explanation for why E4+ experience more PPH; they are exhibiting traits of older age.

Limitations: This paper presents preliminary findings from the first 32 finishers of a larger study. Strengths of this study include a crossover method eliminating the need for a control group. Limitations include small numbers of participants, more women than men in the study, and some differences between the meals that include higher potential salt content with the HFM and a warmed element in the HCM. Most of these participants did not have hypertension, reflecting a healthy volunteer population and may limit generalizability of the results. However, it is interesting that the finding was noted in individual without hypertension, implying that this finding may occur early in E4+ individuals. Future studies could build upon these results to elucidate mechanisms for the E4+ effect on PPH, including absorption studies, hormone levels including insulin, and vascular regulatory mechanisms.

Conclusions

Using a crossover design, we studied the acute effects of high fat and high carbohydrate feeding on post prandial blood pressure in older adults with and without the AD risk gene APOE4. We confirmed that even in physically and cognitively healthy older adults, a significant number of them met criteria for PPH. Individuals who carried at least one copy of the E4+ gene were at higher risk of PPH, and E4+ status also influenced the relationship between age and PPH. Given that guidelines are continuing to emphasize treatment of SBP at lower BPs to best prevent cardiovascular disease endpoints, these types of studies may be important to elucidate the benefits and burdens of such therapies, particularly for cognitive health.

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