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Effect of *ginkgo biloba* on blood pressure and incidence of hypertension in elderly men and women

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Abstract

Background—Accumulating evidence suggests that *ginkgo biloba* is cardioprotective, in part, through its vasodilatory and antihypertensive properties. However, definitive data on its blood pressure-lowering effects in humans is lacking.

Methods—We determined the effects of *ginkgo biloba* extract (240 mg/day) on blood pressure and incident hypertension in 3,069 participants (mean age, 79 yrs; 46% female; 96% White) from the Ginkgo Evaluation of Memory study. We also examined whether the treatment effects are modified by baseline hypertension status.

Results—At baseline 54% of the study participants were hypertensive, 28% were pre-hypertensive, and 17% were normotensive. Over a median follow-up of 6.1 years, there were similar changes in blood pressure and pulse pressure in the *ginkgo biloba* and placebo groups. Although baseline hypertension status did not modify the antihypertensive effects of *ginkgo biloba*, it did influence the changes in blood pressure variables observed during follow-up, with decreases in hypertensives, increases in normotensives, and no changes in pre-hypertensives. Among participants who were not on antihypertensive medications at baseline, there was no difference between treatment groups in medication use over time, as the OR (95% CI) for being a never-user in the *ginkgo biloba* group was 0.75 (0.48–1.16). The rate of incident hypertension also did not differ between participants assigned to *ginkgo biloba* vs. placebo (HR, 0.99, 95% CI, 0.84–1.15).

Conclusions—Our data indicate that *ginkgo biloba* does not reduce blood pressure or the incidence of hypertension in elderly men and women.

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Disclosures
The authors have no conflicts of interest to report.

Keywords

gingko biloba; blood pressure; hypertension; elderly

Introduction

Ginkgo biloba extract is an herbal dietary supplement commonly used for the treatment and prevention of aging-related cognitive decline and dementia.1 Several studies also suggest a cardioprotective effect of *ginkgo biloba* through its antioxidant, antiplatelet, antithrombotic, and vasodilatory properties.2 Furthermore, *ginkgo biloba* may have significant antihypertensive properties as well, providing a possible alternative mechanism for cardiovascular disease prevention. In hypertensive rats treatment with *ginkgo biloba* attenuated the rise in blood pressure (BP), such that systolic BP was 11–21% lower, diastolic BP was 7–10% lower, and mean BP was 28% lower in treated vs. untreated rats.3–7 Interestingly, these BP-lowering effects appeared to occur early in the development of hypertension and were not observed in normotensive rats.

Few studies have investigated the effects of *ginkgo biloba* on BP in humans. Two small studies in young, normotensive subjects showed no change in BP after 1 to 6 weeks of *gingko biloba*.8, 9 In contrast, 3 months of *ginkgo biloba* led to a 6% reduction in systolic BP and a 21% reduction in diastolic BP in a slightly older, pre-hypertensive population.10 The reasons for these contrasting results are likely due, in part, to differences in the treatment duration and study population. Taken together, these findings emphasize the need for a large, randomized controlled trial that can address the effects of *ginkgo biloba* on BP in humans. The Ginkgo Evaluation of Memory (GEM) study provides a unique opportunity to examine this relationship in elderly community-dwelling adults. In the present analysis we hypothesized that participants randomized to the treatment arm would have greater reductions in BP and pulse pressure (PP) than participants randomized to placebo. Based on previous studies in rats and humans, we also hypothesized that these BP-lowering effects would be influenced by the baseline hypertension status.

Methods

Study Population

The GEM study is a double-blind, placebo-controlled, randomized clinical trial evaluating the effectiveness of *ginkgo biloba* (240 mg/day) in the prevention of dementia in older adults over a median follow-up of 6.1 years.11 A total of 3,069 participants were recruited between September 2000 and June 2002 from four clinical centers: Johns Hopkins University, University of California at Davis, University of Pittsburgh, and Wake Forest University. Eligibility requirements included being free of dementia,≥75 yrs of age, a primary English speaker, and able to enroll a proxy. Individuals were excluded if they were demented or taking warfarin, antipsychotic medications, or cholinesterase inhibitors. Individuals who were unwilling to reduce their vitamin E intake to 400 IU/day or stop taking *ginkgo biloba* were also excluded from the trial. Additional exclusions included a history of bleeding disorders, cancer within the past 5 years, congestive heart failure with disability, untreated depression, hospitalization for depression in the past year, and Parkinson's disease. All sites obtained approval from their institutional review boards. Signed informed consent was obtained from GEM study participants and their respective proxies.

Study Intervention

Participants were randomized to either 120-mg of *ginkgo biloba* extract (EGb 761; Schwabe Pharmaceuticals, Karsruhe, Germany) or an identically appearing placebo twice a day. The composition of the active and placebo tablets was confirmed by independent laboratory testing.11 Group assignment was determined by permuted block design by clinical site, and each site used a computer-generated, randomly permuted list to randomize participants. All participants and clinical personnel were blinded to the treatment assignment. Only the study pharmacist who allocated the treatments into batches and the coordinating center personnel who reported to the study Data and Safety Monitoring Board knew which pills were active; however, they were unaware of participant information.

Study Outcomes

The primary outcomes were systolic and diastolic BP, PP, and incident hypertension. BP was measured in the right arm using a standard mercury sphygmomanometer (W.A. Baum Company, Inc., Copiague, NY) with the subject seated and resting quietly for at least 5 minutes. An appropriately-sized cuff was inflated rapidly to 20 mmHg above the palpated systolic pressure and deflated at 2 mmHg/s. The 1^{st}-phase and 5^{th}-phase Korotkoff sounds were used to identify systolic and diastolic BP, respectively. The average of 2 measurements was used in the analysis. PP was calculated as the difference between systolic and diastolic BP. At baseline, individuals were categorized into 3 groups according to guidelines from The Seventh Report of the Joint NationalCommittee on Prevention, Detection, Evaluation, and Treatmentof High Blood Pressure (JNC-7).12 Individuals were classified as hypertensive if any of the following criteria were met: 1) self-reported hypertension and concomitant use of antihypertensive medications; 2) systolic BP≥140 mmHg; or 3) diastolic BP ≥90 mmHg. Individuals were classified as normotensive if they had a systolic BP <120 mmHg or a diastolic BP <80 mmHg. Pre-hypertension was defined as a systolic BP = 120–139 mmHg or a diastolic BP = 80–89 mmHg. The use of antihypertensive medications was assessed at the baseline visit where participants were instructed to bring in all prescription drugs taken in the previous 2 weeks. A trained interviewer entered the name of the drug, dose, and frequency of use in a medications computer system.13 Seated BP and antihypertensive medication use (either on or not on meds) were reassessed every 6 months. Incident hypertension was defined as the start of antihypertensive medications or a 5-mmHg (or 10-mmHg) increase in BP during follow-up such that the participant could be reclassified as “hypertensive” based on JNC-7 guidelines.

Baseline Covariates

The following demographic and health characteristics were assessed at baseline: age, race, sex, education, cigarette smoking status, alcohol consumption, physical activity (based on the question: Do you walk for exercise or pleasure?), cardiovascular disease (includes myocardial infarction, angina, coronary artery bypass surgery, angioplasty, stroke, and transient ischemic attack), and diabetes (based on self-reported physician diagnosis). Body mass index (BMI) was calculated from anthropometric measurements as weight in kilograms divided by height in meters squared.

Statistical Analyses

Analyses were conducted using an intention-to-treat approach in which participants were kept in their randomly assigned groups regardless of their drug compliance. BP analyses were done in the entire study population and stratified by baseline hypertension status. Analysis of variance and chi-square frequency tests were used to compare differences in continuous and categorical variables, respectively, between normotensives, pre-hypertensives, and hypertensives. Mixed models regression was used to determine the

association of changes in systolic BP, diastolic BP, and PP with treatment assignment using all available BP measurements on every participant who came in for a clinic visit. If BP data was not available, the missing values were imputed. Three-way interactions of treatment group x time x gender, race, baseline antihypertensive medication use, and baseline hypertension status were tested in the overall group. In these same models, tests of the two-way interactions between the above factors and time were also examined. Adjusted analyses were performed to account for baseline risk factors associated with changes in BP over time, including initial BP, age, gender, race, education, physical activity, smoking status, alcohol consumption, heart rate, BMI, diabetes, cardiovascular disease, and antihypertensive medication use. Clinical site was forced into the model to control for potential variations in study population between sites. Models with antihypertensive medication use entered as a time-dependent covariate were also explored. To account for the significant effect of baseline medication use on changes in BP variables over time, we performed a secondary analysis excluding participants who were on antihypertensive medications at baseline. Logistic regression was used to compute odds ratios (OR) and 95% confidence intervals (CI) for the association between treatment group and antihypertensive medication use among individuals who were non-users of antihypertensive medications at baseline. Participants were considered “never-users” if they reported no use of antihypertensive medications at baseline and at all follow-up visits. The Cox proportional hazards model was used to compute hazard ratios (HR) for the association between treatment group and incident hypertension. For this analysis, all participants who were hypertensive or on antihypertensive medications at baseline were excluded. Additional Cox regression models were done adjusting for the baseline covariates mentioned above. Statistical significance was set at $p \leq 0.05$.

Results

Baseline Characteristics

Table 1 shows the baseline characteristics of the study population overall and stratified by baseline hypertension status. Among the 3,069 study participants, 54% were hypertensive, 28% were pre-hypertensive, and 17% were normotensive. Hypertensive individuals were more likely to be older, female, and less educated. They also had a higher prevalence of diabetes and cardiovascular disease, a lower heart rate, and a higher BMI. Race, smoking status, alcohol consumption, and physical activity were similar among normotensives, pre-hypertensives, and hypertensives. As reported previously, baseline characteristics did not differ between treatment groups with respect to age, gender, race, education, smoking status, diabetes, cardiovascular disease, BP, or BMI.11 There was also no difference in alcohol consumption (p=0.76), hypertension status (p=0.79), or antihypertensive medication use (placebo: 56.6% vs. *ginkgo biloba*: 57.5%, p=0.58) between treatment groups. There were no significant 3-way interactions with gender (p=0.35–0.52), race (p=0.09–0.16), baseline antihypertensive medication use (p=0.46–0.89), or baseline hypertension status (p=0.29–0.91).

Effect of *Ginkgo Biloba* Supplementation on Changes in Blood Pressure

Table 2 shows the unadjusted mean annual changes in systolic BP and PP by treatment group overall and stratified by baseline hypertension status. We first analyzed all study participants, combining both users and non-users of antihypertensive medications at baseline. Overall, there were similar reductions in systolic BP in the *ginkgo biloba* (p=0.001) and placebo (p=0.01) groups. PP decreased in the *ginkgo biloba* group (p=0.01), but not in the placebo group (p=0.67); however, these changes were not different between groups. There were also similar reductions (p=0.30) in diastolic BP in both treatment

groups: *ginkgo biloba*, −0.1 ± 0.1 mmHg, p=0.03; and placebo, −0.2 ± 0.1 mmHg, p=0.0003).

We also investigated the changes in BP when stratified by baseline hypertension status (Table 2). There were significant 2-way interactions between baseline hypertension status and time for all 3 BP variables (p<0.01). In hypertensives, there were significant reductions in systolic BP, diastolic BP, and PP that were similar between treatment groups (p=0.34–0.97). In normotensives there were significant increases in systolic BP and PP, but no change in diastolic BP. Again, these changes were similar between treatment groups (p=0.09–0.75). In pre-hypertensive individuals, there were no significant changes in any of the BP variables, whether randomized to *ginkgo biloba* or placebo (p=0.12–0.48). As shown in Table 2, the overall and stratified results were similar when analyses were limited to only those individuals who were non-users of antihypertensive medications at baseline. Adjustment for baseline risk factors did not significantly change the results (data not shown). These findings were also similar when antihypertensive medication use was included as a time-dependent covariate.

In logistic regression analyses, we examined the association between treatment group and antihypertensive medication use over time among participants who were non-users at baseline. There were 83 participants who reported being non-users at all 13 follow-up visits (i.e. never-users). Of those, 47 participants were in the placebo group (3.1%) and 36 participants were in the *ginkgo biloba* group (2.4%). The OR (95% CI) for being a never-user in the *ginkgo biloba* group was 0.75 (0.48–1.16), p=0.19. Adjustment for baseline hypertension status had minimal effects. The rate of incident hypertension also did not differ between participants assigned to *ginkgo biloba* vs. placebo (323/462 vs. 310/459; HR, 0.99; 95% CI, 0.84–1.15). A similar HR was found after multivariable adjustment (HR, 1.01; 95% CI, 0.86–1.18). These results were virtually identical whether a 5- or 10-mmHg increase in BP was used. Additionally, we examined whether treatment group was associated with discontinuation of antihypertensive medications. Among hypertensives that were on medications at baseline, 2.0% in the *ginkgo biloba* group and 3.3% in the placebo group went off medications at some point during follow-up and remained off for the duration of the study. This was not different between groups (p=0.15).

Discussion

We examined the antihypertensive effects of *ginkgo biloba* in elderly men and women from the GEM study. The major finding of this analysis was that *ginkgo biloba* had no effect on BP or PP in this population. We found similar reductions in systolic and diastolic BP and PP in the *ginkgo biloba* and placebo groups. Baseline hypertension status did not modify the antihypertensive effects of ginkgo biloba; however, it did influence the changes in BP observed during follow-up. Hypertensives had significant reductions in all three BP variables, while normotensives had significant increases in systolic BP and PP. On the other hand, BP and PP remained fairly stable in pre-hypertensives. These findings are consistent with regression to the mean and were unchanged even after excluding participants on antihypertensive medications at baseline or adjusting for changes in medication use over time. We also found no evidence that *ginkgo biloba* reduces the incidence of hypertension.

Surprisingly, there are only a few studies that have investigated the potential antihypertensive properties of *ginkgo biloba* in humans. Kalus et al. reported no significant differences in systolic or diastolic BP in young (mean age: 23 yrs), normotensive subjects randomized to 240 mg/day of *gingko biloba* for 7 days compared to the placebo group.9 Similarly, Mehlsen et al. reported no differences in BP in a slightly older (median age: 32 yrs), normotensive population after 6 weeks of *gingko biloba* (28.8 mg

ginkgoflavonglucoside and 7.2 mg terpenlactones/day).8 These data are consistent with findings in rat studies, which show that *ginkgo biloba* has no effect on BP in normotensive controls.3–7 In contrast, *ginkgo biloba* has significant BP-lowering effects in hypertensive rats, and this effect occurs early in the development of hypertension. In this regard, one study found that in pre-hypertensive adults aged 21 to 57 yrs, the intake of *ginkgo biloba* (120 mg/day) for 3 months led to a 6% and 21% reduction in systolic and diastolic BP, respectively.10 In our study, *ginkgo biloba* had no effect on BP in elderly pre-hypertensives. However, the lack of a significant change in BP among those with pre-hypertension precludes observing any differences due to treatment. To our knowledge, no other studies have reported the effects of long-term *ginkgo biloba* supplementation on BP in hypertensive individuals or in an older population. Nevertheless, other beneficial effects on the vasculature have been reported after acute and chronic *gingko biloba* intake in humans, including increases in coronary, ocular, and forearm blood flow, improvements in endothelium-dependent vasodilation, and reductions in peripheral vascular resistance.8, 14, 15 This suggests that, despite the absence of an antihypertensive effect of *ginkgo biloba* in the present study, it is possible that other unmeasured markers of vascular health may have actually improved.

It should be noted that the age of the GEM study population could be a factor contributing to the lack of significant findings. Most of the rat studies showing a significant BP-lowering effect of *ginkgo biloba* were conducted in young hypertensive rats (i.e. 5–10 weeks old). However, one study found that 4 weeks of *gingko biloba* was unable to attenuate the rise in BP or PP in 50 week-old hypertensive rats.16 The authors suggested that in elderly hypertensives, long-term *ginkgo biloba* supplementation may not be useful in improving cardiovascular function. Indeed, it is possible that the antihypertensive effects of *ginkgo biloba* may not be evident in elderly persons, particularly those with prolonged exposure to high BP. Moreover, a recent analysis in the REASON study demonstrated that among individuals with uncomplicated hypertension, those with the highest aortic stiffness had the smallest BP reduction in response to treatmenet.15 The authors concluded that aortic stiffness is a major determinant of the effectiveness of antihypertensive therapy. It is possible that increased aortic stiffness may also reduce the antihypertensive effects of *ginkgo biloba*. In the REASON study, PP increased significantly across tertiles of aortic stiffness from 59 mmHg to 68 mmHg. In our study population, the mean PP was 64 mmHg, suggesting that our participants potentially had increased aortic stiffness as well. Taken together, it seems plausible that age-related changes in the vasculature may affect the ability of *ginkgo biloba* to lower BP in elderly individuals.

There were a few limitations in this study. The study population included a select cohort of elderly adults at increased risk for dementia; thus, our results may have limited generalizability. Also, we could not fully control for the effect of antihypertensive medications. Although we did a secondary analysis excluding participants who were on these medications at baseline, over 96% of baseline non-users eventually started taking antihypertensive medications at some point during follow-up. Thus, it is possible that the effects of these medications washed out any potential effect of *ginkgo biloba*. Moreover, there is some indication that *ginkgo biloba* may interact with specific classes of antihypertensive medications to alter their pharmacological effects.17–19 For this reason, we are currently examining the interaction between type of antihypertensive medication and treatment group on BP in the GEM study. There was also no data collected on self-reported hypertension during follow-up. Thus, in our definition of incident hypertension, we could not account for confounding by indication. As such, we may have included participants who were not hypertensive, thereby diluting our ability to find an association with treatment. Nevertheless, these medications affect BP whether prescribed for that purpose or not, and our results were unchanged even after adjusting for medication use over time. These

limitations notwithstanding, this is the first and largest controlled, randomized clinical trial to examine the effects of *ginkgo biloba* on BP. In addition, a commonly-prescribed dose and a standardized formulation of *ginkgo biloba* extract were used in this study. Other strengths include the duration of exposure (median, 6.1 yrs; maximum, 7.3 yrs) and the low drop-out rate (<10%).11

In summary, *ginkgo biloba* was not effective in reducing BP or the incidence of hypertension in elderly men and women in the GEM study. Despite the negative results, this study begins to address an important question regarding the effectiveness of *ginkgo biloba* in improving hemodynamics and vascular function in elderly persons, which is an area of research that has been largely unexplored. Future studies should determine whether these findings are applicable to a slightly younger population (e.g. 60–75 yrs) that is pre-hypertensive or hypertensive and not on BP-lowering medications. Additionally, it would be useful to assess other measures of vascular health, such as endothelial function or arterial stiffness, which could provide cardioprotective benefits even in the absence of reductions in BP.

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APPENDIX – GEM Study Personnel

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Table 1

Baseline characteristics of study participants overall and by baseline hypertension status

Characteristic	Overall	Normotensive (n=523)	Pre-hypertensive (n=881)	Hypertensive (n=1665)	P-value*
Age, yrs	78.6 ± 3.3	78.3 ± 3.1	78.5 ± 3.2	78.8 ± 3.4	0.0008
Female	1418 (46.2)	220 (42.1)	383 (43.5)	815 (49.0)	0.004
Non-White	139 (4.5)	16 (3.1)	36 (4.1)	87 (5.2)	0.09
Education					0.0002
High school or less	110 (36.0)	154 (29.5)	298 (33.8)	652 (39.2)	
Some college	775 (25.3)	146 (27.9)	207 (23.5)	422 (25.4)	
College graduate	480 (15.6)	88 (16.8)	143 (16.2)	249 (14.9)	
Postgraduate	710 (23.1)	135 (25.8)	233 (26.5)	342 (20.5)	
Smoking Status					0.71
Never	1224 (40.7)	212 (41.2)	344 (39.9)	668 (40.9)	
Former	1651 (54.8)	283 (55.0)	484 (56.1)	884 (54.1)	
Current	136 (4.5)	20 (3.9)	35 (4.1)	81 (5.0)	
Alcohol, drinks/week					0.12
0	1286 (42.6)	203 (39.4)	356 (41.0)	727 (44.4)	
0–7	1155 (38.2)	217 (42.1)	345 (39.7)	593 (36.2)	
7–14	286 (9.5)	53 (10.3)	76 (8.8)	157 (9.6)	
>14	294 (9.7)	42 (8.2)	92 (10.6)	160 (9.8)	
Physical activity	2496 (82.1)	429 (83.1)	710 (81.4)	1357 (82.1)	0.72
Diabetes	277 (9.2)	39 (7.5)	59 (6.8)	179 (10.9)	0.001
Cardiovascular disease	786 (25.6)	119 (22.8)	177 (20.1)	490 (29.4)	<0.0001
Heart rate, bpm	67.2 ± 12.0	68.5 ± 11.9	67.1 ± 11.0	66.7 ± 12.6	0.01
BMI, kg/m^2	27.1 ± 4.3	26.4 ± 4.2	26.7 ± 4.0	27.6 ± 4.4	<0.0001
Systolic BP, mmHg	133.0 ± 18.4	110.1 ± 6.9	129.2 ± 5.9	142.2 ±18.2	<0.0001
Diastolic BP, mmHg	68.9 ± 9.9	62.2 ± 7.0	68.3 ± 8.2	71.3 ± 10.4	<0.0001
Pulse Pressure, mmHg	64.1 ± 15.7	47.9 ± 7.9	60.9 ± 9.4	70.8 ± 16.0	<0.0001

Table values are mean ± SD or number (percentage).

*P-value for the comparison across the 3 groups by ANOVA. BMI, body mass index; BP, blood pressure; bpm, beats per minute.

Table 2

Annual changes in systolic BP and PP by treatment group overall and stratified by baseline hypertension status, in all participants and in those who were not on antihypertensive medications at baseline

		Systolic Blood Pressure			Pulse Pressure		
	n[ψ]	Placebo	Ginkgo biloba	Interaction[‖]	Placebo	Ginkgo biloba	Interaction[‖]
All participants	1524/1545	−0.2 (0.1)[§]	−0.3 (0.1)[‡]	0.60	−0.0 (0.1)	−0.2 (0.1)[‡]	0.13
Normotensives	263/260	0.6 (0.2)[†]	0.6 (0.2)[†]	0.75	0.6 (0.1)[*]	0.5 (0.1)[†]	0.38
Pre-hypertensives	429/452	0.1 (0.1)	−0.2 (0.1)	0.12	0.2 (0.1)	−0.1 (0.1)	0.16
Hypertensives	823/833	−0.6 (0.1)[*]	−0.6 (0.1)[*]	0.97	−0.3 (0.1)[‡]	−0.5 (0.1)[*]	0.46
Baseline non-users only	662/656	−0.1 (0.1)	−0.1 (0.1)	0.85	0.2 (0.1)	−0.0 (0.1)	0.22
Normotensive	178/159	0.6 (0.2)[†]	0.6 (0.2)[‡]	0.88	0.7 (0.2)[*]	0.5 (0.2)[‡]	0.37
Pre-hypertensive	292/310	0.1 (0.2)	−0.0 (0.2)	0.51	0.2 (0.1)	0.1 (0.1)	0.34
Hypertensive	192/187	−1.1 (0.3)[†]	−0.9 (0.3)[‡]	0.67	−0.4 (0.2)	−0.6 (0.2)[‡]	0.68

Table values are unadjusted mean (SE).

[ψ]Sample size for each placebo/ginkgo biloba subgroup; Significant change within group,

[*]p≤0.0001,

[†]p≤0.001,

[‡]p≤0.01,

[§]p≤0.05.

[‖]P-value for treatment x time interaction