# Effect of *Ginkgo biloba* Extract on Preexisting Visual Field Damage in Normal Tension Glaucoma

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***Objective:*** To evaluate the effect of *Ginkgo biloba* extract (GBE) on preexisting visual field damage in patients with normal tension glaucoma (NTG).

***Design:*** Prospective, randomized, placebo-controlled, double-masked cross-over trial.

***Participants:*** Twenty-seven patients with bilateral visual field damage resulting from NTG.

***Intervention:*** Patients received 40 mg GBE, administered orally, three times daily for 4 weeks, followed by a wash-out period of 8 weeks, then 4 weeks of placebo treatment (identical capsules filled with 40 mg fructose). Other patients underwent the same regimen, but took the placebo first and the GBE last. Visual field tests, performed at baseline and at the end of each phase of the study, were evaluated for changes.

***Main Outcome Measures:*** Change in visual field and any ocular or systemic complications.

***Results:*** After GBE treatment, a significant improvement in visual fields indices was recorded: mean deviation (MD) at baseline versus MD after GBE treatment, 11.40 ± 3.27 dB versus 8.78 ± 2.56 dB ($t = 8.86$, $P = 0.0001$, chi-square test); corrected pattern standard deviation (CPSD) at baseline versus CPSD after GBE treatment, 10.93 ± 2.12 dB versus 8.13 ± 2.12 dB ($t = 9.89$, $P = 0.0001$, chi-square test). No significant changes were found in intraocular pressure, blood pressure, or heart rate after placebo or GBE treatment. Any ocular and systemic side effects were recorded for the duration of the trial.

***Conclusions:*** *Ginkgo biloba* extract administration appears to improve preexisting visual field damage in some patients with NTG. *Ophthalmology 2003;110:359–364 © 2003 by the American Academy of Ophthalmology.*

Normal tension glaucoma (NTG) is a form of primary open-angle glaucoma in which damage of the optic nerve and visual field are present, despite intraocular pressure (IOP) measurements within statistically normal ranges.[1]

The exact mechanisms of the anatomic and functional damage in NTG are unknown, and debate on the vascular basic (reduced blood flow to the optic nerve) versus the mechanical theory (relatively high IOP) continues.[2]

Because some patients with NTG can continue to have loss of visual field (VF) despite medical therapies or surgical procedures, the pathogenic role of other factors warrants consideration.[3]

An extract from the leaves of the Ginkgo biloba tree (GBE) has been used by patients with peripheral vascular disease and in the treatment of cerebral insufficiency.[4] Several mechanisms of action of GBE have been described: (1) effects on blood circulation, such as vasoregulatory activity and rheological effects (decreased viscosity, antagonistic to platelet activating factor receptors); (2) metabolic changes, for example effects on neuron metabolism (e.g., increased tolerance to anoxia); (3) beneficial effect on neurotransmitter disturbances; and (4) prevention of damage to cell membranes caused by free radicals.[4]

In the past few years, numerous favorable effects of GBE have been reported, although the quality of most of these investigations is questionable. Most recently, it has been shown in a randomized controlled clinical trial that GBE seems to be capable of stabilizing and improving the cognitive performance for from 6 months up to 1 year in patients with Alzheimer's disease.[5]

On the basis of the reported favorable effects of GBE on blood circulation, and considering the possible pathogenetic role of impaired blood flow to the optic nerve in the anatomic and functional damage in NTG, we evaluated the effect of GBE on preexisting damage of VFs of patients with NTG.

## Patients and Methods

From September 1999 through the entire month of December 1999, 27 consecutive patients (54 eyes), 11 men and 16 women

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(mean age, 70.4 years; range, 58–80 years), who had bilateral NTG with progressive damage of the their VFs were recruited for the study. Patients were those who had been referred to the glaucoma Service of Brescia University. Eligibility criteria were as follows: (1) evidence of optic nerve damage associated with VF alterations; (2) IOP 18 mmHg or less without any topical hypotensive therapy (average of the two highest values recorded during diurnal measurements, made from 8 AM to 6 PM, every two hours by Goldmann applanation tonometer); (3) progression of anatomic and functional damage as determined by computerized perimetry and serial stereophotographs of the optic nerve head; (4) experience of the patient in VF testing; (5) normal results of laboratory evaluations, including noninvasive carotid artery studies, complete blood cell count, syphilis serologic tests, and sedimentation rate; (6) no clinical evidence of any neurologic disease; and (7) any consideration of ocular and systemic medications.

This study was approved by the University of Brescia Institutional Review Board, and all patients gave informed consent.

Patients were assigned randomly to one of the two treatments: GBE 40 mg (24% flavinoid glycosides, 6% terpenes; FidiaOftal Spa, Catania, Italy) orally, administered three times daily for 4 weeks, followed by a washout period of 8 weeks, followed by 4 weeks of placebo (identical capsules filled with 40 mg fructose), or the same scheme but with the placebo first. The washout period was determined on the basis of the data in the existing literature.[6,7]

Patients were asked to swallow the capsules whole, so that no difference in taste could be distinguished.

Visual field examinations of both eyes were repeated after each treatment and at the end of the washout period, before starting the next treatment. The baseline VF was considered to be the last of a series of three VF testings, performed 1 week before entry into the study. The IOP and blood pressure were recorded before and after each phase of the study (single measurement of each taken at the same time of the day for all phases of the trial). Randomization to treatment group was performed according to a binary sequence (A–B–A–B, etc.) based on a computer-generated sequence of random numbers; treatment for group A: GBE → washout → placebo, sequence for group B: placebo → washout → GBE.[8] Patients and investigators were masked to the treatment.

All tests were performed using the 24-2 program of Humphrey Visual Field Analyzer II (HFA II, Model 720; Humphrey Instruments, San Leandro, CA) with size III white stimulus under standard conditions using full thresholds with the standard -4 to -2dB single reversal strategy throughout. Each test included in the final analysis met the reliability criteria set by the manufacturer. All VF tests were performed on the same perimeter with best correction for near vision for each patient.

The IOP, blood pressure, and the heart rate were checked every 2 hours from 8:00 AM to 6:00 PM on the same days on which VFs examinations were performed.

Table 1. Characteristics of All Patients Studied

| Variable | Value |
|---|---|
| Number of patients | 27 (27 eyes) |
| Age (years), mean ± 2 SD (range) | 70.4 ± 6.5 (58–80) |
| Gender | 16 female, 11 male |
| IOP (mmHg), mean ± 2 SD (range) | 14.2 ± 2.4 (10–18) |
| Diastolic blood pressure (mmHg), mean ± 2 SD (range) | 72.6 ± 6.2 (60–90) |
| Systolic blood pressure (mmHg), mean ± 2 SD (range) | 119 ± 9.1 (100–135) |
| Heart rate (bpm), mean ± 2 SD (range) | 64.6 ± 7.6 (55–75) |

2 SD = two standard deviations; bpm = beats per minute; IOP = intraocular pressure.

Complete ocular and systemic examinations were performed at the conclusion of each phase of the trial, and any ocular or systemic complications were noted.

Statistical analysis of the data was performed by the chi-square test, comparing visual field indices (mean deviation [MD] and corrected pattern standard deviation [CPSD]), IOP, blood pressure, and heart rate for each phase of the study. The power for each of these tests was more than 0.75. The statistical tests were two-tailed with an $\alpha$ value of 0.05, and the confidence interval was computed at the 95% level using the BMDP computer program (release 7.0; SPSS Inc., Chicago, IL).[8]

For statistical analysis, only the right eye was considered.

## Results

All patients completed the trial, and none reported any differences in taste of the capsules between the two treatment phases of the trial.

Fourteen patients were allocated to group A (sequence: GBE → washout → placebo) and 13 to group B (sequence: placebo → washout → GBE). No significant differences in demographics were recorded between the two groups (Table 1).

In group A (14 eyes of 14 patients), after the GBE phase a statistically significant difference was evident for MD and CPSD when compared with the baseline values (MD baseline vs. MD after GBE, 11.76 ± 4.02 dB vs. 9.29 ± 3.09 dB; $t = 5.53$, $P = 0.0001$, chi-square test; CPSD baseline vs. CPSD after GBE, 11.48 ± 2.09 dB vs. 8.72 ± 2.16 dB; $t = 7.49$, $P = 0.0001$, chi-square test). After the washout period and the placebo phase, no significant modifications were detected when compared with the baseline (Table 2).

In group B, after the placebo phase and after the washout period, no significant modifications in MD or CPSD were noted

Table 2. Visual Field Indices after Each Phase of the Study (Patients are Divided in Two Groups According to Sequences of Treatment)

| Visual Field Indices | Group A (14 Eyes of 14 Patients) | | | | Group B (13 Eyes of 13 Patients) | | | |
|---|---|---|---|---|---|---|---|---|
| | *Baseline* | *Ginkgo biloba Extract* | *Washout* | *Placebo* | *Baseline* | *Placebo* | *Washout* | *Ginkgo biloba Extract* |
| MD (dB) | 11.76 ± 4.02 (6.35–18.67) | 9.29 ± 3.09 (4.95–14.45) | 11.92 ± 4.13 (6.54–17.87) | 11.82 ± 3.66 (7.12–17.45) | 11.01 ± 2.33 (7.54–15.24) | 11.12 ± 2.16 (7.52–14.32) | 11.13 ± 2.18 (8.31–15.67) | 8.24 ± 1.81 (6.32–11.32) |
| CPSD (dB) | 11.48 ± 2.09 (5.86–13.54) | 8.72 ± 2.16 (4.98–12.11) | 11.35 ± 2.31 (6.12–14.76) | 11.11 ± 2.45 (5.00–14.89) | 10.33 ± 2.07 (5.98–12.34) | 10.45 ± 2.11 (6.67–13.00) | 10.05 ± 2.00 (6.12–12.21) | 7.50 ± 1.96 (4.87–10.34) |

Group A sequence of treatment: GBE → washout → placebo; group B sequence of treatment: placebo → washout → GBE.
All data presented are mean ± two standard deviations (range).
CPSD = corrected pattern standard deviation; dB = decibel; MD = mean deviation.

Table 3. Statistical Analysis of Visual Field Indices of Eyes before and after Treatment with *Ginkgo biloba* Extract

| Visual Field Indices | Baseline (n = 27 eyes)* | After *Ginko biloba* Extract Treatment (n = 27 eyes)* | *t* Value† | *P* Value† |
|---|---|---|---|---|
| MD | 11.40 ± 3.27 dB (range, 6.35–18.67 dB) | 8.78 ± 2.56 dB (range, 4.95–14.45 dB) | 8.86 | 0.0001 |
| CPSD | 10.93 ± 2.12 dB (range, 5.86–13.54 dB) | 8.13 ± 2.12 dB (range, 4.87–12.11 dB) | 9.89 | 0.0001 |

CPSD = corrected pattern standard deviation; dB = decibel; MD = mean deviation.
*Mean ± two standard deviations (range).
†Chi-square test (two tailed).

when compared with the baseline values. After the GBE phase, a significant improvement of the MD and CPSD values when compared with the baseline and the placebo phase values was noted (MD baseline vs. MD after GBE, 11.01 ± 2.33 dB vs. 8.24 ± 1.81 dB; $t = 7.03$, $P = 0.0001$, chi-square test; CPSD baseline vs. CPSD after GBE, 10.33 ± 2.07 dB vs. 7.50 ± 1.96, $t = 6.32$, $P = 0.0001$, chi-square test; Table 2).

Statistical analysis of the data revealed a significant reduction of the MD and CPSD values when all eyes of groups A and B were pooled as compared with their pooled baseline values (Table 3).

No significant modifications in IOP, blood pressure, or heart rate were noted after either placebo or GBE phases when the patients were pooled (Table 4).

No ocular or systemic side effects were noted in any patient during the trial.

## Discussion

Our results suggest that GBE administration can effect an improvement in preexisting visual field damage in some individuals with NTG.

The exact explanation for this effect is not clear, but it has been demonstrated that GBE is able to increase blood flow in the ophthalmic artery in healthy subjects.[6] We could hypothesize that our small series of NTG patients might have benefitted from this effect. As a matter of fact, vascular components, such as reduced blood flow to the optic nerve, seem to have an important role in the genesis and progression of visual field damage in NTG.[1]

In the past decade, elucidation of risk factors for glaucomatous damage, other than those that are IOP dependent, has become an area of increasingly active investigation. These risk factors include systemic hypotension, including positional or nocturnal hypotension,[9–13] cardiovascular disease,[12,14–16] vasospasm (migraine, Raynaud's disease),[17–24] defective vascular autoregulation,[25] autoimmune disease,[26,27] hemorheologic abnormalities,[16,28] and cerebral microvascular ischemia.[29]

*Ginkgo biloba* extract has numerous properties that theoretically should be beneficial in treating non–IOP-dependent mechanisms in glaucoma. Its multiple beneficial effects, including increased ocular blood flow, and its antioxidant activity, platelet activating factor inhibition, nitric oxide inhibition, and neuroprotective activity combine to suggest that GBE could play a major role in the treatment of glaucoma.[7]

Another possible explanation of the beneficial effects of GBE in NTG patients may be the ability of GBE to improve cognitive functions.[5] This effect has been demonstrated in patients with cerebral vascular insufficiency[4] and has been attributed to increased cerebral blood flow. It has been demonstrated that, in NTG patients, cerebral small-vessel ischemia is more common than in normal subjects.[29] It is thus reasonable to assume that GBE administration improves VF indices via increased cerebral blood flow, thus improving ocular blood flow, and thereby improving retinal sensitivity, as well as concentration and alertness.[7]

Another concept to be explored carefully is the possible neuroprotective action of GBE. In the present series, because of the short-term follow-up, we cannot comment regarding this mechanism of action. Because the biologic activities of GBE include increasing neuronal tolerance to anoxia, having a favorable effect on neurotransmitter disturbances, and preventing damage of cell membranes caused by free radicals, it seems to have a potential role in the improvement of visual function.[7] More extended follow-up and a larger series of patients may better define the effects of GBE.

The limited duration of our study does not allow comment on how long the effects of GBE administration last. The finding that improvement in VF indices was not maintained after 8 weeks of washout in group A (sequence of treatment, GBE → washout → placebo) suggests that GBE has an a limited duration of action when discontinued and may have to be administered chronically to maintain its effect. The duration of effect and optimal administration schedule for GBE treatment has to be investigated in future studies of NTG patients.

In the present study, no ocular or systemic adverse events related to the use of GBE were recorded, although this may

Table 4. Intraocular Pressure and Blood Pressure Responses to Placebo and *Ginkgo biloba* Extract (n = 27 patients; n = 27 eyes)

| Variables | Baseline* | Placebo* | *P* Value† | Baseline after Washout* | *Ginko biloba* Extract* | *P* Value† |
|---|---|---|---|---|---|---|
| IOP (mmHg) | 14.2 ± 2.4 | 14.3 ± 2.1 | 0.204 | 14.6 ± 2.1 | 14.7 ± 2.0 | 0.173 |
| Diastolic blood pressure (mmHg) | 72.6 ± 6.2 | 71.6 ± 8.5 | 0.384 | 73.6 ± 8.3 | 74 ± 7.8 | 0.719 |
| Systolic blood pressure (mmHg) | 119 ± 9.1 | 118 ± 7.2 | 0.550 | 118 ± 6.9 | 117 ± 8.4 | 0.484 |
| Heart rate (bpm) | 64.6 ± 7.6 | 63.0 ± 8.1 | 0.960 | 62.6 ± 7.0 | 61.6 ± 6.7 | 0.189 |

bpm = beats per minute; IOP = intraocular pressure.
*Mean ± two standard deviations.
†Chi-square test, two tailed.

be the result of the limited duration of the trial. These results are also in accordance with those of a long-term randomized clinical trial in which no significant difference in the incidence of adverse events was found when GBE-treated patients were compared with a control group.[5]

In conclusion, a long-term prospective, placebo-controlled, randomized trial that takes into account the effects of GBE on visual field, optic nerve characteristics, and ocular blood flow is warranted to ascertain if GBE truly is of benefit as a systemic treatment for NTG.

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## Discussion
## by
## Robert Ritch, MD

The maidenhair tree, *Ginkgo biloba,* is the sole survivor of the oldest order of trees, having originated in the Permian Era approximately 250 million years ago. Leaf extracts have been used in Chinese traditional medicine since 3000 BCE, originally for treating asthma and bronchitis.[1] *Ginkgo biloba* extract (GBE) contains more than 60 bioactive compounds, approximately 30 of which are found nowhere else in nature. These include flavone glycosides (flavonoids), terpene lactones (ginkgolides and bilobalide), proanthocyanidines, and numerous other compounds.[2]

*Ginkgo biloba* extract has been claimed to be effective in a variety of disorders, including decreasing cognitive function,[3–8] cerebrovascular insufficiency,[9,10] peripheral vascular disease,[11,12] asthma, and atopic dermatitis.[13,14] It appears to have many properties applicable to the treatment of non–pressure-dependent risk factors for glaucomatous damage.

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*Gingko biloba* extract protects against free radical damage and lipid peroxidation in various tissues and experimental systems. Its antioxidant potential is comparable with water-soluble antioxidants such as ascorbic acid and glutathione and lipid soluble ones such as alpha-tocopherol and retinol acetate.[15]

*Ginkgo biloba* extract preserves mitochondrial metabolism and adenosine triphosphate production in various tissues and partially prevents morphologic changes and oxidative damage associated with mitochondrial aging.[16–20] It inhibits inducible nitric oxide synthase activity,[21] platelet activating factor activity,[22,23] and neurotoxicity induced by glutamate.[24,25] It protects against ischemia-reperfusion injury in the brain[26] and myocardium[27–29] and exhibits neuroprotective effects and inhibits apoptosis in cell culture systems[30–34] and in animal models of neurologic disease.[35–37] *Ginkgo biloba* extract improves both peripheral and cerebral blood flow,[38] decreases blood viscosity,[39] increases erythrocyte deformability,[39] and inhibits platelet aggregation[40,41] and thrombus formation.[42]

In the eye, GBE reduces ischemia-reperfusion injury in the retina[43] and inhibits preretinal proliferation in experimental tractional retinal detachment.[44] It has been reported to protect against lipoperoxidation,[45] against damage resulting from argon laser photocoagulation,[46] against the progression of diabetic retinopathy,[47] and against light-induced damage.[48] In elderly patients with symptoms of cerebrovascular insufficiency, GBE has been reported to improve automated visual field indices.[49] We have shown in an earlier double-masked crossover study of normal volunteers that GBE significantly increased the end diastolic blood velocity in the ophthalmic artery.[50] The average change from baseline was 24%, which is substantial when it is considered that the coefficient of variation for the ophthalmic artery and diastolic velocity measurement is 6%.[50]

Quaranta et al examined 27 patients with untreated normal tension glaucoma and progressive visual field damage in a double-masked, crossover study of 4 weeks of treatment with either GBE versus placebo with an 8-week washout period between arms of the study. Group A patients were treated first with GBE, whereas group B patients were treated first with placebo. The authors state that no significant differences in demographics were recorded between the two groups, but this is not indicated in Table 1, which does not divide the groups.

Full threshold visual field examinations were repeated after each treatment and at the end of the washout period, before starting the next treatment. In each group of patients, mean deviation and corrected pattern standard deviation improved significantly after treatment with GBE but not after placebo. The effect, at least in group A, in which it was measured, was not maintained after discontinuation of GBE. It would also be useful to know not just the range of mean deviation and corrected pattern standard deviation before and after treatment with GBE, but more information concerning absolute differences. Could the authors divide patients into high responders and low responders, and would there be any demographic differences between such groups?

Visual field improvement theoretically could result from improved retinal ganglion cell function or improved cognitive abilities. Either of these effects could occur secondary to improved blood flow to the eye, the brain, or both to a neuroprotective effect of GBE. Further studies are needed both to verify the results presented here and to determine by what mechanisms GBE may benefit patients with glaucoma. The authors are to be commended in embarking along this innovative avenue of research. *Ginkgo biloba* extract deserves further investigation for its potential in the treatment of glaucoma as well as other ischemic ocular diseases.

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