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Clinical science

Effects of nicotinamide supplementation in normal-tension glaucoma: a crossover placebo-controlled randomised clinical trial

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ABSTRACT

Background/Aims The neuroprotective effect of nicotinamide (NAM) supplementation has been demonstrated in both animal models and clinical trials. We conducted a trial to assess whether oral NAM improves retinal function in normal-tension glaucoma (NTG) participants receiving intraocular pressure (IOP)-lowering therapy.

Methods Fifty-three NTG participants (untreated IOP ≤18 mm Hg) were enrolled in a double-masked, placebo-controlled crossover randomised clinical trial. Participants were randomly assigned to receive either oral placebo or NAM, followed by crossover without a washout period. Each treatment was administered for 12 weeks (NAM/placebo 1 g/day for 6 weeks, then 2 g/day for the subsequent 6 weeks). Retinal function was evaluated using full-field electroretinography and visual field testing.

Results After 12 weeks, the amplitude changes of the photopic negative response in peak-to-trough (PhNRPT) and the B-wave were significantly greater in the NAM group (3.121±3.968 and 2.112±3.220 µV, respectively) compared with the placebo group (0.996±4.190 and 0.305±3.279 µV, respectively; p=0.045 and p=0.032). PhNRPT improved beyond twice the 95% coefficient of variation in 29.0% of the NAM group and 19.3% of the placebo group. No significant intergroup differences were observed in changes in mean deviation, pattern SD or visual field index after 12 weeks.

Conclusion Oral NAM supplementation in NTG participants induced functional improvement, as measured by PhNRPT and B-wave amplitude. Given that NTG is characterised by lower IOP, which may show a weaker correlation with electrophysiological activity and a slower progression rate compared with high-tension glaucoma, further long-term studies are needed to clarify the effects of NAM in this population.

Trial registration number NCT06078605.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Nicotinamide (NAM) supplementation has demonstrated neuroprotective effects in animal models and early clinical trials, possibly by improving retinal ganglion cell function.
⇒ Normal-tension glaucoma (NTG) is a subtype of glaucoma characterised by progressive optic nerve damage despite relatively low intraocular pressure (IOP).
⇒ To date, no studies have directly evaluated the neuroprotective effects of NAM in participants with NTG.

WHAT THIS STUDY ADDS

⇒ This study evaluated the effect of oral NAM supplementation on retinal function in NTG participants already receiving IOP-lowering therapy.
⇒ It demonstrates that NAM treatment significantly enhances photopic negative response and B-wave amplitudes, suggesting a direct functional benefit independent of any IOP reduction.
⇒ Oral NAM supplementation at a dosage of 2g/day in NTG participants demonstrated no serious side effects.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ These findings support the use of NAM as an adjunctive neuroprotective therapy in the management of NTG.
⇒ They highlight the importance of targeting retinal ganglion cell health beyond IOP control, encouraging future long-term studies and possibly expanding treatment strategies for patients with glaucoma.

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INTRODUCTION

Glaucoma is characterised by the progressive dysfunction and loss of retinal ganglion cells (RGCs). Intraocular pressure (IOP) reduction remains the only validated strategy to slow disease progression across diverse stages and risk profiles.[1–4] Yet, in many cases, glaucoma progresses despite notable reductions in IOP, observed frequently in real-world clinical settings. Given the complex aetiology and diverse risk factors associated with the disease, there is a critical need for developing treatments focused on neuroprotection.

Mitochondrial dysfunction and the resultant oxidative stress have been shown to be early and critical factors contributing to the loss of RGCs in

glaucoma.[5] Nicotinamide adenine dinucleotide (NAD) is a vital cofactor for mitochondrial ATP production, and patients with glaucoma have decreased serum nicotinamide levels (NAM; the amide of vitamin B_3 and precursor for NAD),[6] suggesting an association between systemic NAD levels and glaucoma susceptibility. Enhancing retinal NAD levels through dietary NAM supplementation or overexpressing the NAD-producing enzyme *NMNAT1* or *NMNAT2* (terminal enzymes for NAD synthesis from NAM) has significantly preserved RGC function in animal models of glaucoma.[7–9] Based on these findings, recent studies have examined the effects of NAM, both alone and in conjunction with other nutritional supplements, revealing potential short-term improvements in inner retinal function and visual field (VF) sensitivity.[10 11]

In normal-tension glaucoma (NTG), glaucomatous damage occurs despite IOP remaining within the statistically normal range, indicating that this level of IOP may not be optimal for the optic nerve in susceptible individuals.[12] It is likely that other factors—such as cardiovascular/neurovascular conditions, impaired ocular blood flow, oxidative stress and endothelial dysfunction—interact with IOP to contribute to the pathogenesis of NTG.[13 14] These observations highlight a significant unmet need for neuroprotective agents that could contribute to slowing disease progression beyond the known benefits of lowering IOP.

To date, no randomised controlled studies have assessed the neuroprotective potential of NAM specifically in patients with NTG. We aimed to investigate whether the functional benefits previously associated with NAM supplementation could also be observed in participants with treated NTG.

METHODS

This study was registered on *clinicaltrials.gov* (NCT06078605) and followed the Consolidated Standards of Reporting Trials reporting guideline.

Study design and enrolment of participants

This study was a prospective, double-masked, randomised, crossover clinical trial conducted in South Korea between September 2022 and March 2024. Participants were recruited from the CHA Bundang Glaucoma outpatient clinic. The study enrolled adult participants (≥19 years), who had been diagnosed with early-to-moderate primary open-angle glaucoma, indicated by a VF mean deviation (MD) better than −12 dB, and possessed a best-corrected visual acuity (BCVA) of at least 20/80. No upper limit was set for baseline VF MD. Eligibility criteria required pretreatment IOP to range from 8 to 18 mm Hg, measured using Goldmann applanation tonometry (GAT). Additionally, participants needed a reliable VF test (SITA-Fast 24-2, HFA II-750i, Carl Zeiss Meditec, Germany) within the previous year, demonstrating <33% fixation losses, false positives and false negatives. When both eyes were eligible, only one eye per participant was randomly selected. All participants received IOP-lowering medications as prescribed by their treating glaucoma specialist, and these treatments remained unchanged throughout the study. Participants were withdrawn if their IOP exceeded 18 mm Hg on two or more occasions. The diagnostic criteria for glaucoma and detailed exclusion criteria are provided in the online supplemental text.

Participants attended a baseline visit (visit 1) and four subsequent visits every 6 weeks (±2 weeks), for a total trial duration of 24 weeks with two 12-week treatment phases (NAM and placebo) in a crossover design. At each visit, a standardised clinical evaluation was conducted, including BCVA using the Snellen chart, IOP measurement via GAT, blood pressure monitoring (HEM-7322, Omron Healthcare, Japan), slit-lamp examination and electroretinogram (ERG). At visits 1, 3 and 5, VF (SITA-Fast 24-2, HFA II-750i) was conducted. The circumpapillary retinal nerve fibre layer thickness (cpRNFL) was assessed using Spectralis SD-OCT (Heidelberg Engineering, Dossenheim, Germany). For safety assessment, routine blood tests—including complete blood count, standard metabolic assessment and urinalysis—were conducted at visits 1, 3 and 5. Liver function parameters such as total bilirubin, aspartate aminotransferase, alanine aminotransferase and alkaline phosphatase were included.

Agents

Participants were randomised 1:1 to the intervention-first or placebo-first group using a pregenerated SAS randomisation table. Participants in the intervention group received an accelerated dosing regimen to improve tolerability comprising a 6-week course of NAM (Mitovita, 0.5 g NAM tablet, Hanlim Pharm, Seoul, Korea) of 1.0 g/day followed by 6 weeks of 2.0 g/day (1.0 g twice a day, morning and evening). While previous studies in Western populations have used doses up to 3 g/day,[10 11] reports of adverse events—including drug-induced liver injury in an underweight Asian participant—highlight the need for caution in dose selection,[15] and informed our decision to limit the maximum NAM dose to 2 g/day.

Placebo pills were manufactured to match the shape and colour of the active agents, as well as the number of pills taken on each visit. After 12 weeks, participants crossed over without washout, as any residual effects of NAM were considered negligible based on prior findings showing no carry-over effect.[10]

To assess adherence, participants returned remaining tablets at each visit for manual counting. Adherence rate (%) was calculated as the number of tablets actually taken divided by the number of tablets prescribed, multiplied by 100. An adherence rate of at least 70% was considered acceptable.

Clinical testing of retinal function

Full-field ERG was performed using the RETeval system (LKC Technologies, Gaithersburg, Maryland, USA), a portable device employing skin electrodes,[16] which were chosen for their ease of use, participant comfort and reduced susceptibility to blink-related artefacts during repeated testing.[17 18] Prior to testing, the pupils were dilated with topical 0.5% tropicamide and 0.5% phenylephrine hydrochloride, and full dilation was confirmed before adaptation to ambient illumination. The stimulus protocol involved red flashes (1.0 cd·s/m², 4 ms, 621 nm) on a constant blue background light (10 cd/m², 470 nm), with the flash intensity selected based on prior studies indicating that photopic negative response (PhNR) structure is reliably identified at this intensity.[19–21] The results were expressed as percentages based on age-matched normative values provided by the manufacturer. To improve the reliability of outcome measures, all exams—including VF and ERG—were double-checked and repeated at least once if the initial test was deemed unreliable. The average of the repeated measurements was used for the final analysis.

The photopic negative response from peak to trough (PhNRPT) amplitude was measured from the B-wave peak to the PhNR trough (figure 1A), a method that has been reported to exhibit high reproducibility.[22] Detailed procedures and analysis methods for ERG are provided in the online supplemental text.

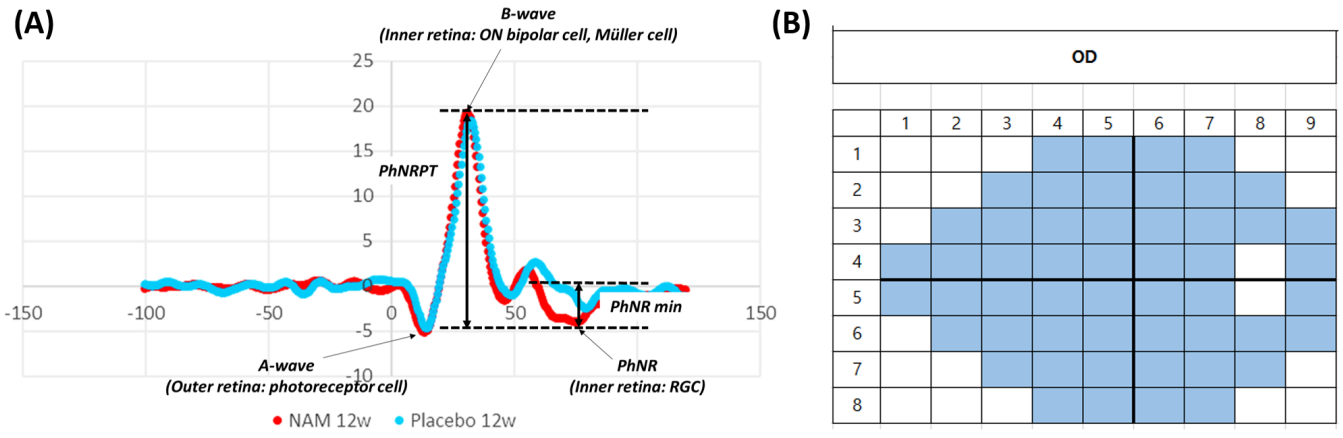

Figure 1 Electroretinogram (ERG) and visual field parameters for outcome analysis. (A) ERG parameters. Photopic negative response from peak to trough (PhNRPT) was measured from the peak of B-wave to trough of negative wave after B-wave. (B) Pointwise sensitivity comparison sheet for visual field test parameters. Note that all 52 locations were compared with baseline data in each visit, respectively. NAM, nicotinamide; PhNR, photopic negative response; ON, On-center; RGC, retinal ganglion cell; OD, oculus dexter

Data analysis

The quality of ERG data was assessed independently of the randomisation group in a masked manner. The final analyses were performed on ERG waveforms that demonstrated a stable baseline and minimal recording noise. Criteria for a stable baseline and minimal noise are provided in the online supplemental text. To exclude the possible confounders on ERG parameters such as high myopia, inconsistent pupil dilation, etc, only recordings in which the B-wave amplitude was <30% of the manufacturer's normative value were included in the final analysis.

VF parameters were analysed using pointwise sensitivity comparison sheets (figure 1B), with all 52 test locations compared with baseline values at each subsequent visit. Improvement of pointwise sensitivity was defined as the number of test points exhibiting a sensitivity increase >10 dB.

Study objectives

The primary outcome was the change in RGC function, assessed by ERG parameters after 12 weeks of NAM versus placebo, specifically PhNRPT, measured from B-wave peak to PhNR trough. Due to the short treatment duration, VF indices were considered secondary outcomes, including changes in MD, pattern SD (PSD), visual field index (VFI) and sensitivity-improved points in total and pattern deviation.

Statistical analysis

The sample size was determined based on a prior study reporting a mean difference of 5.03 μV in PhNR values between groups.[10] A total of 40 eyes was planned for enrolment, which, after accounting for an anticipated 25% attrition rate, was estimated to provide 90% statistical power to detect a significant difference between the groups at a two-sided α level of 0.05.

The primary analysis set consisted of participants who completed all study visits. Statistical analyses were performed using GraphPad Prism (GraphPad Software, Boston, Massachusetts, USA) by a statistician masked to treatment allocation. For each outcome, the within-participant sum was derived by adding the baseline-adjusted changes observed under placebo and NAM conditions. These totals were then compared between randomisation groups using a two-sample t-test. To assess potential period effects, the within-participant difference (NAM-placebo) was analysed using linear regression, with adjustments made for the corresponding baseline values. Changes in PhNRPT were also compared with the 95% coefficient of repeatability (COR), which was 2.33 μV in this study set. This value was derived from the baseline ERG data of the 52 participants, using the formula: mean±1.96×SD.

RESULTS

A total of 53 participants were randomised into the study, of which 46 completed the study (figure 2). All participants were ethnically Korean and had been on IOP-lowering treatments prior to enrolment. The baseline characteristics of participants included in the safety set analysis (n=52, 57.0±11.1 years, 52% female) are presented in table 1. Adherence was high for both treatments, with over 90% adherence observed for NAM, indicating good tolerability across both low and high doses. The number of participants and the reasons for exclusion from the final analysis are shown in online supplemental figure 1. No significant differences were observed between the placebo and NAM groups in either IOP or cpRNFL thickness (online supplemental figure 2 and table 1).

At the 12-week visit, the amplitude changes in the PhNRPT and the B-wave was significantly greater in the NAM treatment (3.121±3.968 µV and 2.112±3.220 µV, respectively) compared with the placebo (0.996±4.190 µV and 0.305±3.279 µV, respectively), with p values of 0.045 and 0.032, respectively (figure 3A-D). Improvements in PhNRPT exceeding twice the 95% COR were observed in 29.0% of the NAM group and 19.4% of the placebo group (p=0.554). However, the PhNR/B-wave ratio at the 12-week visit did not significantly differ between the two groups (0.012±0.087 in NAM vs 0.028±0.102 in placebo, p=0.507). No significant changes were noted in 6 weeks with low-dose NAM or placebo. In addition, no effect was observed on ERG measures of outer retinal function, including A-wave amplitudes and implicit times (figure 3E,F).

No significant differences were observed in changes to global VF indices, including MD, PSD and VFI, after 12 weeks (figure 4). The mean number of pointwise improvements on total deviation and PSD was higher in NAM-treated eyes (1.146±1.49 and 1.146±1.53) compared with placebo-treated eyes (0.829±1.20 and 0.781±1.13); however, the difference did

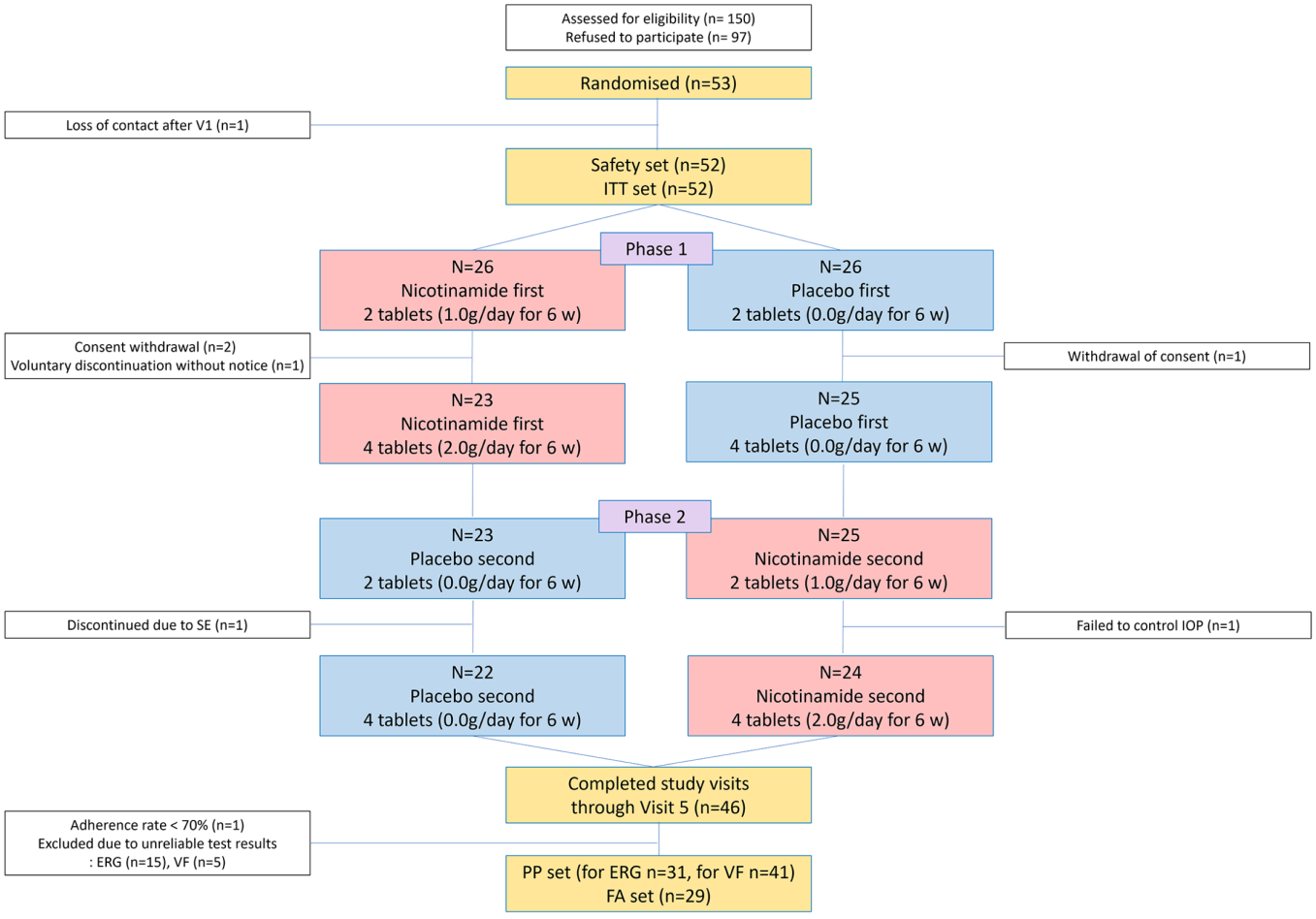

Figure 2 Consolidated Standards of Reporting Trials diagram. All participants were randomised into two groups (group 1, NAM first; group 2, placebo first) and then followed to crossover without a washout period after administration of study drugs for 12 weeks. ERG, electroretinogram; FA, full analysis; ITT, intention-to-treat; NAM, nicotinamide; PP, per-protocol, VF, visual field.

not reach statistical significance (p=0.29 and p=0.22, respectively). There was no evidence of carry-over and period effects (online supplemental table 2).

No serious adverse events were reported throughout the study. In the NAM-treated group, one participant each reported conjunctival hyperaemia, cystitis, cough and rash. One participant discontinued the study after experiencing a headache during the placebo phase; the symptoms resolved completely on cessation of treatment. No cases of gastrointestinal discomfort or elevations in liver function tests greater than two-fold of the upper limit of normal were observed.

DISCUSSION

In this randomised clinical trial, participants with IOP-treated NTG demonstrated significant improvement in inner retinal function after 12 weeks of NAM supplementation compared with placebo. Although changes in global VF indices were not different between groups, the number of pointwise improvements in total deviation and pattern deviation was greater in NAM-treated eyes, without reaching statistical significance, suggesting functional enhancement. Importantly, no NAM-related serious adverse events were observed.

Previously, Hui *et al* demonstrated the neuroprotective effects of NAM in IOP-treated glaucoma participants in a randomised, placebo-controlled trial.[10] They observed significant improvement in PhNR after 12 weeks of NAM supplementation, as well as an improvement in VF MD. Additionally, NAM combined with another nutritional supplement (pyruvate) showed a significant enhancement in visual function compared with placebo.[11] Both previous studies included participants with glaucoma regardless of their untreated IOP, whereas our study exclusively enrolled participants with baseline IOP within the normal range. Our results further support the potential benefit of NAM supplementation in patients with NTG, at least over the short term, providing a rationale for larger and long-term clinical trials to establish stronger evidence.

We observed a significant increase in amplitude in RGC function, as measured by the PhNRPT, and in the B-waves, which primarily reflect the activity of ON-bipolar cells and Müller cells.[23] Although glaucoma has traditionally been viewed as a disease mainly characterised by RGC loss, emerging evidence indicates that other cell types may also be involved early in the pathogenesis.[24] Shen *et al* demonstrated that bipolar cell function was significantly impaired before detectable RGC dysfunction in three distinct experimental models, suggesting that the B-wave could serve as a potential early diagnostic marker for glaucoma.[25] In the DBA/2J mouse, an inherited model of glaucoma, Müller cells exhibit early reactivity even when RGCs remain structurally intact, suggesting a potential role for these glial cells in the pathogenesis of glaucoma.[26] Supporting this, reactive Müller cells have also been observed in patients with glaucoma.[27] Further studies are required to determine whether

Table 1 Baseline demographics of total participants (safety set, n=52)

Parameters	NAM first (n=26)	Placebo first (n=26)	Total (n=52)	P value
Sex				
Male, n (%)	8 (30.77)	17 (65.38)	25 (48.08)	
Female, n (%)	18 (69.23)	9 (34.62)	27 (51.92)	0.0125*
Age (years)				
Mean±SD	56.96±11.83	57.00±10.54	56.98±11.10	0.9902†
Range	31–80	31–79	31–80	
Disease duration (mon)				
Mean±SD	78.50±42.94	86.88±43.66	82.69±43.08	0.5519‡
Range	15–222	19–192	15–222	
IOP (mm Hg)				
Mean±SD	14.23±2.05	14.50±2.23	14.35±2.11	0.5766†
Range	10–17	8–17	8–17	
Visual acuity (logMAR)				
Mean±SD	0.021±0.045	0.015±0.035	0.018±0.040	0.5983†
Range	0–0.097	0–0.155	0–0.155	
Height (cm)				
Mean±SD	163.83±10.45	165.12±9.63	164.48±9.97	0.6473‡
Range	150.8–186.6	149.1–182.3	149.1–186.6	
Weight (kg)				
Mean±SD	63.80±11.72	68.52±10.82	66.16±11.42	0.1373†
Range	47.2–93.5	48.6–90.6	47.2–93.5	
SBP (mm Hg)				
Mean±SD	125.85±9.99	129.35±7.10	127.60±8.76	0.3000‡
Range	98–138	107–139	98–139	
DBP (mm Hg)				
Mean±SD	77.85±7.13	79.04±7.17	78.44±7.11	0.3182‡
Range	62–89	61–89	61–89	
PhNRPT (µV)				
Mean±SD	24.40±5.84	23.28±6.61	23.77±6.21	0.8080†
Range	16.74–35.03	9.58–36.64	9.58~36.64	
A-wave (µV)				
Mean±SD	−6.15±1.37	−5.50±1.18	−5.79±1.29	0.3010†
Range	−9.40~−4.39	−7.59~−2.34	−9.40~−2.34	
B-wave (µV)				
Mean±SD	19.19±5.35	16.80±5.43	17.84±5.44	0.3570†
Range	13.23~31.95	6.64~26.02	6.64~31.95	
MD (dB)				
Mean±SD	−4.94±3.16	−4.90±3.53	−4.92±3.32	0.6470†
Range	−11.46~0.18	−11.7~0.44	−11.7~0.44	
PSD (dB)				
Mean±SD	5.34±3.18	5.88±4.21	5.63±3.73	0.5040†
Range	1.30~11.38	1.35~14.53	1.30~14.53	
VFI (%)				
Mean±SD	91.16±6.17	89.55±7.91	90.29±7.11	0.7440†
Range	78~99	68~99	68~99	

*P value for χ^2 test.
†P value for two-sample t-test.
‡P value for Wilcoxon rank sum test.
DBP, diastolic blood pressure; IOP, intraocular pressure; MD, mean deviation; NAM, nicotinamide; PhNRPT, photopic negative response from peak to trough; PSD, pattern SD; SBP, systolic blood pressure; VFI, visual field index.

the B-wave changes observed in our study are clinically relevant and reproducible in patients with NTG.

However, it is important to note that despite the significant increases in both PhNRPT and B-wave amplitudes observed in the NAM-treated group, the PhNR/B-wave ratio did not differ significantly between the NAM and placebo groups. This suggests that the observed enhancement in PhNRPT amplitude was accompanied by a proportional increase in inner retinal activity, rather than indicating a selective improvement in RGC function alone. While this may reflect a broader retinal response to NAM supplementation, it also underscores the complexity of interpreting ERG changes in isolation. Further studies are

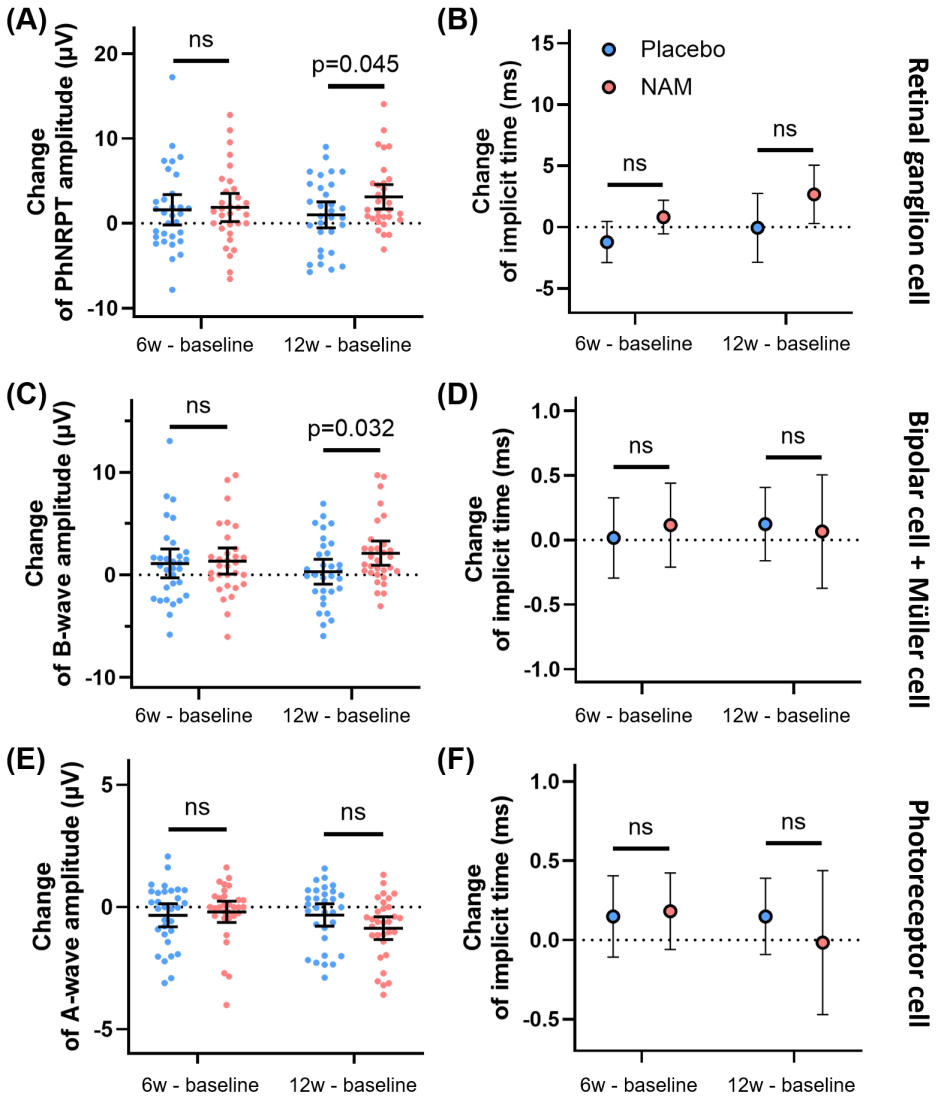

Figure 3 Comparison of electroretinogram parameters between NAM-treated eyes (n=31) and placebo-treated eyes (n=31). (A, B) Amplitude change of PhNRPT in NAM-treated eyes showed significant improvement compared with placebo-treated eyes (p=0.045). Implicit time change of PhNRPT showed no difference between the two groups. (C, D) Amplitude change of B-wave in NAM-treated eyes showed significant improvement compared with placebo-treated eyes (p=0.032). Implicit time change of B-wave showed no difference between the two groups. (E, F) Amplitude and implicit time changes of A-wave showed no difference between the two groups. Error bars represent the 95% CIs. NAM, nicotinamide; ns, not significant; PhNRPT, photopic negative response from peak to trough.

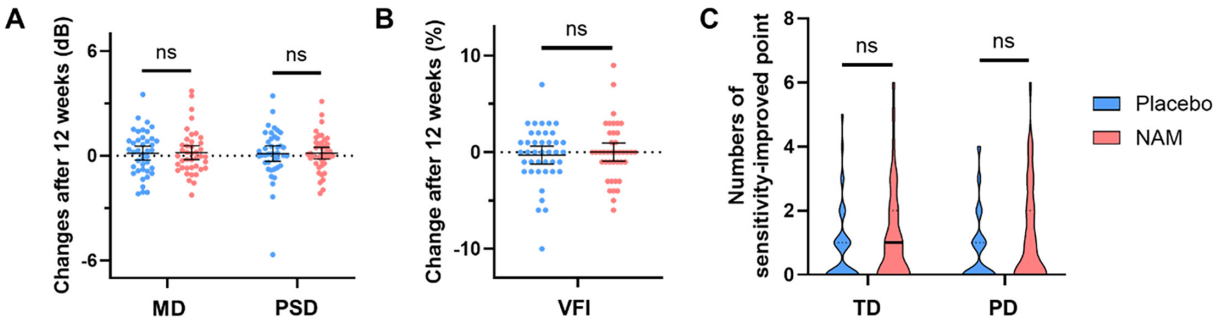

Figure 4 Comparison of perimetric value changes between placebo-treated and NAM-treated eyes (n=41). (A, B) Changes in MD, pattern SD and VFI showed no difference between the two groups. (C) Median value of pointwise improved point number in NAM-treated eyes was higher than that in placebo-treated eyes (measured in TD plot); however, no statistical significance was noted. Error bars represent the 95% CIs. MD, mean deviation; NAM, nicotinamide; ns, not significant; PD, pattern deviation; PSD, pattern SD; TD, total deviation; VFI, visual field index.

warranted to explore whether such parallel improvements reflect true functional recovery across multiple retinal cell types or represent different responsiveness in the NTG population.

In our study, despite improvements in retinal function, we did not observe statistically significant differences in VF outcomes. Although VF remains the gold standard for assessing visual function in clinical and research settings, it should be noted that the rate of progression in NTG is generally slower than that observed in glaucoma with elevated IOP.[28 29] Consequently, long-term follow-up may be necessary. In addition, detecting subtle yet clinically meaningful changes in VF may require a greater number of tests, use of alternative testing algorithms or clustering-based analytical approaches, which should be considered in future research.

The NAM dosage used in our study was lower than that in previous studies,[10 11] considering the generally smaller body size of Asians. Based on the limited data shown, the body mass index (BMI) of our participants seems lower (online supplemental text). Given that individual factors such as BMI and body size may influence NAM absorption, metabolism and plasma NAD levels through pharmacokinetic and pharmacodynamic variability.[30] The optimal NAM dose that maximises neuroprotective efficacy while minimising side effects in patients with glaucoma with small body size remains to be determined. Furthermore, it is notable that the previous study demonstrating significant improvement in VF combined NAM with another nutritional supplement, pyruvate. Given that pyruvate has recently been recognised as a key contributor to energy metabolism,[31] future studies are warranted to investigate the potential synergistic effects of combined supplementation.

There are several study limitations. First, given the short-term nature of our study, it remains unclear whether NAM supplementation at the current dose can lead to sustained functional improvements over longer periods. Ito *et al*[32] reported that metabolomic changes following oral administration of NAM 200 mg lasted for approximately 24 hours, suggesting that the systemic effects of NAM may be transient. Further studies are needed to determine whether the changes observed in ERG will persist over the long term with continued NAM supplementation or if they are transient, returning to baseline despite ongoing treatment. Second, although the final sample size exceeded the number estimated in the power calculation, the study population remained relatively small. Importantly, of the 46 participants who completed the study, 15 (32.6%) were excluded due to unreliable ERG, which may have reduced statistical power and affected the accuracy of effect estimation. In addition, the exclusion of these participants may have introduced bias, potentially compromising the generalisability of the primary findings. Third, our ERG protocol used fixed flash luminance. In the study by Hui *et al*,[10] ERG amplitudes across the luminance series were modelled using a saturating hyperbolic function to generate a luminance-response function. This function may vary depending on factors such as age, glaucoma severity and individual differences. In addition, we used skin electrodes, which may offer lower signal amplitudes compared with corneal electrodes. Accordingly, our fixed-luminance protocol and use of skin electrodes may have limited sensitivity in detecting subtle or early functional changes. Moreover, as pupil size was not quantitatively measured, subtle intervisit variations may have affected retinal illuminance and consequently influenced ERG amplitudes. Fourth, we did not include a washout period, based on prior evidence suggesting that the systemic metabolic effects of NAM are short-lived.[32] Our post hoc analysis revealed no evidence of a carry-over effect. Nonetheless, the lack of a predefined washout period remains a methodological limitation and should be taken into account when interpreting the results of the second treatment phase. Lastly, we did not confirm metabolomic changes via blood assays after NAM supplementation. As baseline NAD levels and responses to NAM vary across individuals—affected by age, sex, ethnicity and other factors[32]—future studies with metabolomic profiling are needed to clarify treatment response and guide optimal dosing.

In conclusion, NAM supplementation resulted in early and measurable improvements in inner retinal function among participants with NTG already receiving IOP-lowering treatment. These findings support prior experimental research suggesting a neuroprotective role for NAM in glaucoma and highlight the need for long-term studies to determine its potential in slowing disease progression.

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Competing interests PW is an inventor on an awarded US patent held by The Jackson Laboratory for nicotinamide treatment in glaucoma ('Treatment and Prevention of Ocular Neurodegenerative Disorder', US11389439B2). All other authors declare no competing interests.

Patient consent for publication Not applicable.

Ethics approval The institutional review boards of CHA Bundang Medical Center approved this study (CHAMC 2022-04-064-039), which adhered to the tenets of the Declaration of Helsinki. Written informed consent was obtained from all participants prior to enrolment.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request. Data analysed in this study will be made available on reasonable request to the corresponding author, provided that the request is supported by a valid scientific or ethical rationale.

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