Molecular Vision 2025; 31:351-357 <http://www.molvis.org/molvis/v31/351>
Received 11 June 2025 | Accepted 1 October 2025 | Published 3 October 2025

Nitazoxanide reduced inflammatory markers and mitochondrial changes in human retinal endothelial cells grown in high glucose

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Purpose: To determine whether nitazoxanide (NZT) can increase mitochondrial nuclear retrograde regulator 1 (MNRR1) in retinal endothelial cells (RECs) grown in normal or high glucose and thereby reduce inflammation.
Methods: We used control and diabetic human retinal protein samples, control and diabetic mouse retinal samples, and RECs grown in normal (5 mM) and high (25 mM) glucose protein samples to explore levels of MNRR1, high mobility group box 1, interleukin 1β, tumor necrosis factor α, and Tom20 by western blotting. We used immunostaining to localize MNRR1 in the retina. We also used a Seahorse XF^{e}24 Bioanalyzer to measure the oxygen consumption rate in RECs under different conditions. Some cells were treated with NZT to increase MNRR1 levels.
Results: MNRR1 protein levels were reduced in the diabetic retina of both humans and mice. MNRR1 was localized to RECs. RECs grown in normal or high glucose and treated with NZT had significantly higher MNRR1 levels. NZT reduced inflammatory markers in RECs grown in high glucose. NZT increased the oxygen consumption rate in RECs grown in high glucose, which was associated with an increase in Tom20.
Conclusions: MNRR1 is reduced in the diabetic retina. NZT increased MNRR1 levels in RECs. NZT protected RECs grown in high glucose by reducing inflammatory mediators and mitochondrial dysfunction and increasing mitochondrial mass. NZT may offer a new therapeutic option for diabetic retinopathy.

Diabetic retinopathy remains the leading cause of blindness in working-age adults despite decades of research on potential mechanisms. Reactive oxygen species (ROS) [1], inflammation [2], and glucose control [3] play a key role in the disease and its progression. ROS, stemming primarily from mitochondrial dysfunction [4], are a key driver of retinal damage in diabetes [5]. In addition to overproduction of ROS, less efficient mitochondrial DNA repair and structural damage to mitochondrial cristae have been observed [6]. A consequence of the increased ROS produced by mitochondria in diabetic retinopathy is increased inflammatory mediator activity [7]. Furthermore, changes in mitochondrial energy homeostasis are linked to many of the events associated with diabetic retinopathy [8]. Additionally, epigenetic changes to mitochondrial proteins have been associated with retinal damage in diabetic animals [9].

A novel player linked to both mitochondrial actions and inflammation is mitochondrial nuclear retrograde regulator 1 (MNRR1; also called CHCHD2, AAG10, or PARK22) [10]. MNRR1 is an ~18-kDa nuclear-encoded protein; under normal physiologic conditions, it is imported into the intermembrane space of mitochondria, where it regulates the oxidative stress response, cellular migration and differentiation, and mitochondrial cristae structure [11]. It can also enter the nucleus, where it acts as a transcription factor for hundreds of genes by binding a conserved oxygen-responsive promoter element (ORE). Among genes regulated by MNRR1 are cytochrome *c* oxidase subunit 4 isoform 2 (*COX4I2*) and several stress-related genes [11,12]. In the presence of cellular stress, increased levels of MNRR1 promote the mitochondrial unfolded protein response and mitophagy [12], whereas reduced levels impair mitochondrial respiration. MNRR1 can be phosphorylated on Tyr 99 by Abl2 kinase to enhance the interaction between MNRR1 and COX to stimulate cellular respiration [11]. Reduction of MNRR1 lowers cell proliferation in non–small cell lung carcinoma [13], and loss of MNRR1 sensitizes cells to cancer drugs [14].

MNRR1 has been linked to inflammation [15], Parkinson's disease [10], and Niemann-Pick disease type C1 [16]. In experimental hyperlipidemia, the drug nitazoxanide (NZT), which stimulates MNRR1 production, was protective, leading to reduced hepatic steatosis in hamsters and mice [17]. Similarly, MNRR1 is deficient in the livers of mice in a

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mouse model of Niemann-Pick disease type C1, a lysosomal storage disorder, and is able to stimulate NPC1 synthesis to reduce disease-related actions [16].

MNRR1 levels are reduced in a mouse model of intra-amniotic inflammation-induced preterm labor. In this model, NZT increased MNRR1 levels and abrogated preterm birth, demonstrating that MNRR1 prevented placental inflammation and reduced TNFα actions [15,18]. NZT is a treatment approved by the US Food and Drug Administration (FDA) for diarrhea caused by parasites [19]. However, its use has been expanded experimentally to other disease conditions. For example, NZT has been shown to be an antiatherosclerotic drug through its effects on mitochondrial uncoupling in ApoE knockout mice [20]. In this study, the authors also studied macrophage cell lines and found that NZT inhibited the NLRP3 inflammasome [20]. In the amyloid precursor protein/presenilin 1 transgenic mouse model of Alzheimer's disease, studies show that NZT reduced inflammation, blocked tau hyperphosphorylation, and decreased senile plaque formation [21]. In a model of rheumatoid arthritis, treatment with NZT reduced interleukin (IL) 6, tumor necrosis factor α (TNFα), and IL-1β levels, as well as ameliorated bone erosion [22]. T lymphocytes obtained from 50 type 2 diabetic patients treated with NZT had reduced levels of IL-1β, IL-6, IL-2, IL-10, and IL-12 in peripheral bone mononuclear cells, showing that NZT may reduce inflammatory markers in diabetic patients [23]. Based on previous work showing a role for mitochondrial dysfunction and inflammation in the diabetic retina, we hypothesized that MNRR1 levels would be reduced in the diabetic retina and retinal endothelial cells (RECs) and that retinal function thus could be improved by treatment with NZT.

METHODS

Human participants: Dr. Mohamed Al-Shabrawey (Oakland University) provided postmortem retinal samples from five nondiabetic control donors and five donors with diabetic retinopathy (both type 1 and type 2). Patients had various stages of diabetic retinopathy and had diabetes for greater than 10 years. The postmortem eyes were obtained from the Eversight Eye Bank (Ann Arbor, MI). Dr. Al-Shabrawey received approval for these samples from Oakland University. This study followed the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Oakland University (5/9/23; IRB-FY2023–292). Samples and information were evaluated by Oakland University and deemed not human research on May 9, 2023, for the study entitled "Molecular and Cellular Mechanisms of Diabetic Retinopathy." Since these samples are deidentified and collected postmortem, the institutional review board of Oakland University deemed them not considered human research. These samples were processed for protein detection by western blotting, as we have done in the past [24].

Diabetic mice: C57BL/6 mice were purchased from Jackson Laboratories (Bar Harbor, ME). Diabetes was induced by 5 days of streptozotocin injections (60 mg/kg, intraperitoneally) at 2 months of age [25]. Glucose levels >250 mg/dl were considered diabetic. At 6 months of diabetes, five control and five diabetic mice were sacrificed for analysis [26]. No animals died before reaching the 6-month time point, and no insulin was given. Mice were allowed free access to water and food and kept at a constant temperature for all experiments. Streptozotocin-treated mice did not gain weight at the same rate as control mice, but all were healthy at the time of sacrifice. Streptozotocin mice all had glucose levels over 250 mg/dl at sacrifice. Mice were checked weekly for health and, at the time of euthanasia, were euthanized by CO_2 overdose and cervical dislocation. All mouse experiments were approved by the Wayne State University Institutional Animal Care and Use Committee and adhered to the Association for Research in Vision and Ophthalmology animal care guidelines. Mouse retinas were collected on a slide for immunostaining or placed into a centrifuge tube with lysis buffer for protein analyses.

Immunostaining of mouse retina: After confirmation of death, the eyes were removed and placed in 4% paraformaldehyde in phosphate-buffered saline (PBS) for 6 h. Whole globes were transferred into 0.1 M PBS with 30% sucrose overnight for cryoprotection, followed by cryosectioning at 10 µm. Cryosections were collected and stored at −20 °C for further analysis. Slides were rinsed in PBS and placed into 5% bovine serum albumin (prepared in 1× PBS, 0.1% TWEEN-20 [PBST]) for 1 h at room temperature to block nonspecific staining, followed by incubation with mouse anti-CD31 conjugated to CoralitePlus488 (1:200; Proteintech, Rosemont, IL) and rabbit anti-MNRR1 conjugated to CoraLite594 (1:200; Proteintech) overnight at 4 °C. Slides were then rinsed in PBS, mounted with Vectashield vibrance with DAPI (Vector Labs, Newark, CA), and examined on a Cytation C10 microscope (Agilent, Santa Clara, CA) at 20× magnification.

Primary human RECs: Primary human RECs were purchased from Cell Systems Corporation (Kirkland, WA). Cells were grown in Cell Systems medium (normal glucose [5 mM] or high glucose [25 mM]) supplemented with microvascular growth supplement, 10 µg/mL gentamycin, and 0.25 µg/mL amphotericin B (Invitrogen, Carlsbad, CA) on attachment factor-coated dishes. Cells were grown in high glucose for a minimum of 5 days, with most dishes in culture for up to 10

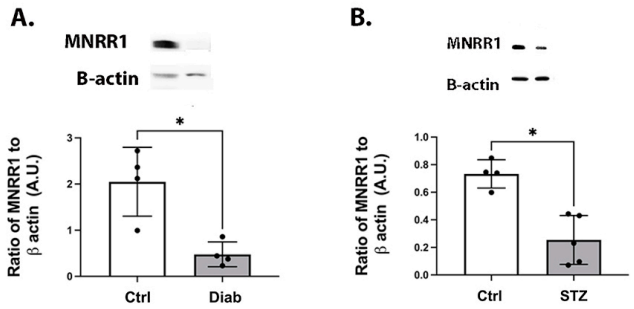

Figure 1. MNRR1 levels in whole retinal lysates from control and diabetic patients. Retinal lysates were separated on a sodium dodecyl sulfate–polyacrylamide gel electrophoresis gel and probed for MNRR1 and β-actin. Gel images and their quantitation are shown. (**A**) Control and (**B**) diabetic mice. *$p < 0.05$ versus ctrl measured by *t* test. n = 5 for all groups.

days. Cells were quiesced by incubation in high- or normal-glucose medium without microvascular growth supplement for 24 h before experimental use. All cells were used before passage 5. Some cells in each glucose condition were treated with 20 µM NZT for relevant experiments.

Cellular oxygen consumption measurements: Cellular oxygen consumption was measured with a Seahorse XFe24 Bioanalyzer (Agilent). Cells were plated at a concentration of 3×10^4 per well the day before treatment, and basal oxygen consumption was measured 48 h after treatment as described [18,27].

Western blotting: Cell culture lysates were collected in lysis buffer containing protease and phosphatase inhibitors. Equal amounts of protein were separated onto a precast tris-glycine gel (Invitrogen) and blotted onto a nitrocellulose membrane. After blocking in TBST (10 mM Tris-HCl buffer, pH 8.0, 150 mM NaCl, 0.1% Tween-20) and 5% (w/v) bovine serum albumin, the membranes were treated overnight with primary antibodies against CHCHD2 (MNRR1; 19,424-1-AP; Proteintech, 1:500), NLRP3 (AB263899, 1:500; Abcam, Cambridge, UK), HMGB1 (10,829-1-AP, 1:500; Proteintech), IL-1B (AB9722, 1:300; Abcam), TNFα (17,590-1-AP, 1:400; Proteintech), Tom20 (1:500; Cell Signaling Technology, Danvers, MA), or β-actin (Santa Cruz Biotechnology, Santa Cruz, CA), followed by incubation with secondary antibodies (anti-rabbit-HRP; Promega, Madison, WI) for 0.5 to 1 h. Antigen-antibody complexes were detected with a chemiluminescence reagent kit (Thermo Scientific, Pittsburgh, PA), and data were acquired using an Azure C500 imager (Azure Biosystems, Dublin, CA). Western blot data were assessed with Image Studio Lite software. A representative blot is shown for each treatment group.

Statistics: All experiments were repeated a minimum of three times, and the data are presented as mean ± SEM. Data were analyzed by a nonparametric Kruskal-Wallis one-way analysis of variance, followed by Dunn's test with *p* values <0.05 considered statistically significant. For groups of two, a *t* test was used.

RESULTS

MNRR1 was reduced in the diabetic retina: Since diabetic retinopathy is associated with increased inflammation, we explored levels of MNRR1 in the retina of human donors with both type 1 and type 2 diabetes, as well as in diabetic mice. Figure 1A shows that, compared to control patients, MNRR1 levels are decreased significantly (>4-fold) in whole retinal lysates from patients with diabetes. All retinal protein samples were from diabetic patients with >10 years of diabetes and with either nonproliferative or proliferative retinopathy. In 6-month diabetic mice, levels of MMRR1 were significantly reduced (>3-fold) compared to control mice (Figure 1B).

MNRR1 was expressed in retinal endothelial cells: To determine whether MNRR1 is located in RECs, we performed immunostaining for MNRR1 in the retina. The yellow staining (merge) in Figure 2 shows that MNRR1 (red) is expressed in retinal endothelial cells (CD31, green).

NZT increased MNRR1 levels in RECs grown in high glucose: To quantify our immunostaining, we grew primary human RECs for 1 week in normal (5 mM, NG) or high (25 mM, HG) glucose. Some cells in each condition were treated with 20 µM NZT (to increase MNRR1) for 24 h. Cells were collected and lysates stained for MNRR1 levels. Figure 3 shows that MNRR1 levels were significantly reduced in HG, and the reduction was significantly reversed by NZT

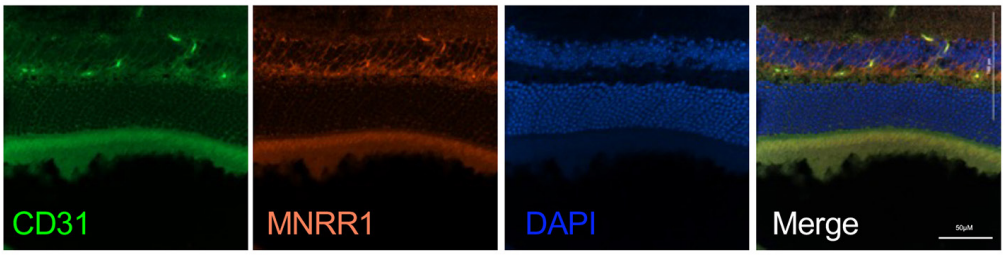

Figure 2. Cellular location of MNRR1. MNRR1 (red) is localized in endothelial cells (CD31, green). DAPI staining shows nuclei. The merged image shows colocalization (yellow) of MNRR1 in endothelial cells. Scale bar is 50 µm.

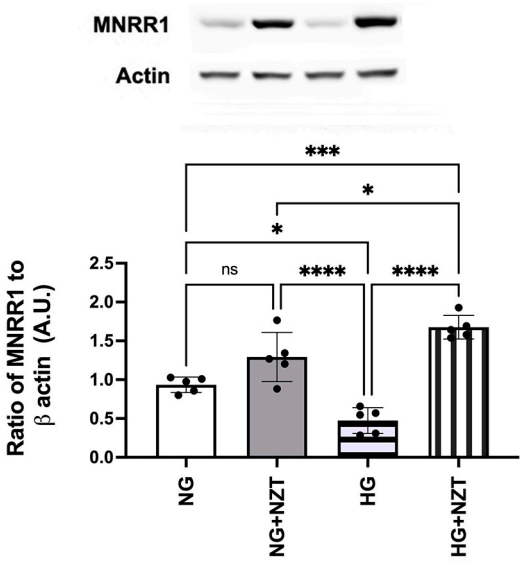

Figure 3. Effect of nitazoxanide and glucose concentration on MNRR1 levels. Cell lysates of control and NZT (20 µM)–treated RECs grown in normal (NG, 5 mM) or high (HG, 25 mM) glucose were separated on a sodium dodecyl sulfate–polyacrylamide gel electrophoresis gel and probed for MNRR1 and β-actin. Gel images and their quantitation are shown. *$p < 0.05$ versus NG, #$p < 0.05$ versus HG by one way-analysis of variance. n = 4.

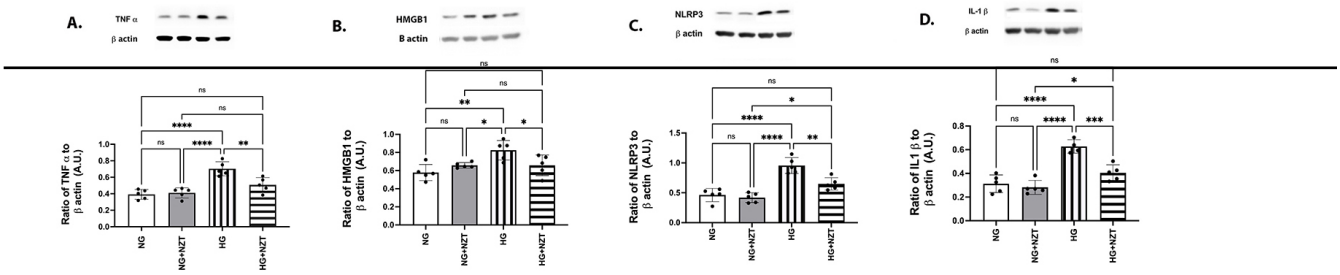

Figure 4. Effect of nitazoxanide and glucose concentration on inflammatory mediators. Lysates of RECs grown in normal glucose (NG) and high glucose (HG) ± NTZ were separated on a sodium dodecyl sulfate–polyacrylamide gel electrophoresis gel and probed for markers of inflammation. Gel images and their quantitation are shown. (**A**) TNFα, (**B**) HMGB1, (**C**) NLRP3, and (**D**) IL-1β. *$p < 0.05$ versus NG, #$p < 0.05$ versus HG assessed by one-way analysis of variance. n = 4.

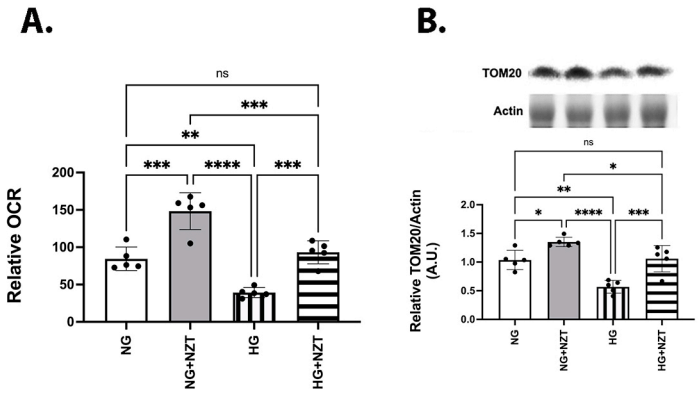

Figure 5. Effect of nitazoxanide and glucose concentration on mitochondrial properties. **A**. Relative OCR levels were measured in a Seahorse XFe24 Bioanalyzer for RECs grown in normal (5 mM) or high (25 mM) glucose alone or treated with NZT. *$p < 0.05$ versus NG, #$p < 0.05$ versus HG by one-way analysis of variance (ANOVA). n = 3. **B**. Lysates of RECs grown as in (A) were separated on a sodium dodecyl sulfate–polyacrylamide gel electrophoresis gel and probed for Tom20 protein. *$p < 0.05$ versus NG, #$p < 0.05$ versus HG by two-way ANOVA. n = 3.

treatment. This also shows that MMRR1 levels in cells grown in NG were also increased by NZT treatment.

NZT reduced inflammatory mediators in RECs cultured in high glucose: Since MNRR1 levels were increased by NZT in cultured RECs, we evaluated the effect of NZT on inflammatory mediators in RECs grown in high glucose. Figure 4 shows that the levels of TNFα (A), high mobility group box 1 (HMGB1) protein (B), NLRP3 (C), and IL-1β (D) were significantly increased in cells grown in HG. In all four conditions, 20 µM NZT treatment of RECs grown in HG significantly reduced the inflammatory mediators. Although NZT increased MNRR1 in RECs in NG, we did not observe NZT-stimulated decreases in the basal levels of inflammatory mediators in the absence of HG; however, NZT reduced the HG-promoted increases.

NZT improved mitochondrial actions in RECs: Since MNRR1 regulates mitochondrial respiration, we wanted to determine if the reduced levels of MNRR1 in diabetic mice resulted in reduced respiration. To do so, we measured oxygen consumption rate (OCR) in RECs grown in NG or HG (1 week) alone or treated with 20 µM NZT for 24 h before harvest. We found that OCR was reduced in RECs grown in HG, whereas it was significantly increased in cells treated with NZT (Figure 5A). To examine the mechanism for the NZT-promoted increase in OCR, we examined mitochondrial mass by measuring the outer membrane mitochondrial protein Tom20. We found that NZT increased mitochondrial mass at both glucose concentrations (Figure 5B), in agreement with our previous finding that NZT promotes mitochondrial proliferation [12].

DISCUSSION

We previously showed that MNRR1 levels were reduced in several disease models containing mitochondrial dysfunction, such as in Nieman-Pick syndrome [16] and lipopolysaccharide-induced preterm birth [15]. In each case, increasing MNRR1 expression, either genetically or pharmacologically, improved the phenotype under study. We show here in RECs grown in high glucose that levels of MNRR1 were also reduced, which was associated with increased inflammatory markers [26,28-30].

The prior observations on the benefit of boosting MNRR1 levels genetically caused us to seek drugs that would enhance its expression. We showed that NTZ could improve the phenotype in several disease models, including preterm birth in mice [15]. Thus, we examined here the effect of NTZ in diabetic retinopathy. Although the connection between inflammation and mitochondrial dysfunction is well established in diabetes and its complications, less is known about regulation of the connecting pathways. Several previous studies from our laboratory and others have demonstrated increased inflammatory mediators in RECs grown in high glucose [24,26,29-32]. Additionally, several decades of research have linked mitochondrial dysfunction to diabetic retinopathy [4,33,34]. Since MNRR1 has been linked to both inflammation and mitochondrial functions, we examined the expression of MNRR1 in the retinal vasculature. We found that it is expressed—primarily in retinal endothelial cells—and, using both human and mouse diabetic models, we found that MNRR1 levels are reduced.

Given previous studies showing that NZT can increase MNRR1 levels, improve mitochondrial function, and reduce markers of inflammation [12,18], we examined its effects in RECs. We found that NZT significantly increased MNRR1 levels in RECs grown in normal and high glucose. Correlated with increased expression of MNRR1 in RECs grown in both low and high glucose, NZT also reduced inflammation and improved mitochondrial function. Although its mechanism of action was not explored here, the findings of improved mitochondrial function in REC agree with other studies showing that increased levels of MNRR1 promote homeostatic pathways such as the mitochondrial unfolded protein response and mitophagy [12].

There are limitations to our findings. We used a relatively small number of human and mouse samples for these studies. We also tested only one dose of NZT in vitro and in vivo. While we focused on RECs due to our immunostaining results, other retinal cell types should be included in future analyses. We also only did short-term studies; however, since diabetic retinopathy is a chronic disease, longer-term studies are warranted. Future studies will need to test the utility of NZT in chronic diabetic mouse retinas, as well as further explore its mechanism of action.

Conclusions: We show that the mitochondrial stress regulator MNRR1 is expressed in retinal endothelial cells and that its level is reduced in the retina from diabetic human and mouse samples. Furthermore, treatment with NZT increases MNRR1 in RECs, reducing markers of inflammation and improving mitochondrial function.

ACKNOWLEDGMENTS

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. Author Contributions: MA provided the human samples. YJ performed the western blotting work; NP did mitochondrial work and edited the text; LG evaluated experiments and edited the text, JJS designed the experiments and wrote the text. Funding: These studies were funded by R01EY030284 (JJS), P30EY04068 Core grant (LDH, PI of Core grant), US Army Medical Research Command (award W81XWH2110402) and the Henry L. Brasza endowment at Wayne State University (LG), an unrestricted grant from Research to Prevent Blindness, and R01EY030054 (MA).

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Articles are provided courtesy of Emory University and The Abraham J. & Phyllis Katz Foundation. The print version of this article was created on 3 October 2025. This reflects all typographical corrections and errata to the article through that date. Details of any changes may be found in the online version of the article.