



ORIGINAL ARTICLE

Effect of Antioxidants in Arresting the Progression of Diabetic Retinopathy and Ascertaining the Morphological Changes in the Red Blood Cells as Oxidative Stress Marker: A Pilot Study

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Abstract

Background: Oxidative stress plays a vital role in the development of diabetes and its complications like retinopathy. Free radical generation in diabetic patients is also responsible for alterations in RBC morphology. This study aims to assess the effect of α -tocopherol (vitamin E) and ascorbic acid (vitamin C) in arresting the progression of diabetic retinopathy and uses red blood cell (RBC) morphology as a biomarker of oxidative stress. **Materials and methods:** This interventional, randomized, open-label pilot study was conducted on 60 adult patients with non-proliferative diabetic retinopathy (NPDR) at a tertiary ophthalmic hospital. Patients were randomized into two groups (n=30 each). The control group received standard antidiabetic treatment, while the study group received add-on therapy with vitamin C 500 mg and vitamin E 400 mg twice daily for 12 weeks. Assessments were performed at baseline and every 4 weeks, with a 4-week post-treatment follow-up. **Results:** There was a statistically significant reduction in fasting blood glucose in the study group compared to control at 12 weeks (ANCOVA $p < 0.001$). The study group showed a highly significant reduction in crenated RBCs with Heinz bodies (from 80.40% to 7.20%, $p < 0.001$) versus minimal change in control (82.57% to 82.33%). Hemoglobin and total RBC count increased significantly in the study group only ($p < 0.001$). **Conclusions:** Supplementation with vitamins C and E as add-on therapy arrested progression of NPDR, improved visual acuity, normalized RBC morphology, and improved hematological parameters. These findings support the role of oxidative stress in diabetic retinopathy and the potential disease-modifying effect of antioxidants.

Keywords: Diabetic retinopathy, Oxidative stress, Antioxidants, Vitamin C, Vitamin E, Red blood cell morphology, Heinz bodies

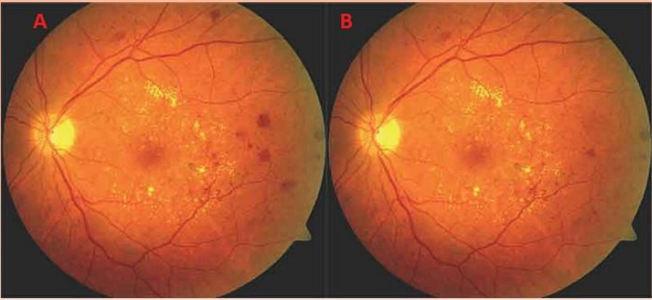
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Graphical Abstract


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Background
Oxidative stress plays a vital role in the development of diabetes and its complications like retinopathy. Free radical generation in diabetic patients is also responsible for alterations in RBC morphology. This study aims to assess the effect of α -tocopherol (vitamin E) and ascorbic acid (vitamin C) in arresting the progression of diabetic retinopathy and uses red blood cell (RBC) morphology as a biomarker of oxidative stress.

Fundus images showing non-proliferative diabetic retinopathy, A- Before treatment, B-After treatment



Methods
This interventional, randomized, open-label pilot study was conducted on 60 adult patients with non-proliferative diabetic retinopathy (NPDR) at a tertiary ophthalmic hospital. Patients were randomized into two groups (n=30 each). The control group received standard antidiabetic treatment, while the study group received add-on therapy with vitamin C 500 mg and vitamin E 400 mg twice daily for 12 weeks. Assessments were performed at baseline and every 4 weeks, with a 4-week post-treatment follow-up.



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Conclusions Supplementation with vitamins C and E as add-on therapy arrested progression of NPDR, improved visual acuity, normalized RBC morphology, and improved hematological parameters. These findings support the role of oxidative stress in diabetic retinopathy and the potential disease-modifying effect of antioxidants.

Introduction

Diabetes mellitus is a chronic metabolic disorder characterized by hyperglycemia, glycosuria, hyperlipidemia, and negative nitrogen balance due to defects in insulin secretion and/or action. Globally, an estimated 422 million adults are living with diabetes mellitus, of which type-II diabetes makes up about 85–90% of all cases [1–3]. In India, diabetes affects more than 62 million people, which is more than 7.1% of the adult population [4–6]. Among its complications, diabetic retinopathy is a major sight-threatening condition leading to blindness [7]. Nearly all patients with type I diabetes develop retinopathy within 15 years, while in type II diabetes the prevalence increases with disease duration: approximately 50% after 10 years, 70% after 20 years, and 90% after 30 years [8–10].

Oxidative stress, defined as an imbalance between free radical production and antioxidant defence [11,12]. Free

radicals are products of normal cellular metabolism and can oxidize biomolecules leading to tissue injury [13,14]. Chronic hyperglycemia increases reactive oxygen species (ROS) generation [15,16], which triggers lipid peroxidation and produces inflammatory mediators such as F₂-isoprostanes [17–19]. These isoprostanes promote insulin resistance, antagonize insulin action, and reduce nitric oxide bioavailability, leading to vasoconstriction and tissue ischemia [20, 21].

Red blood cells (RBCs), being enucleated and highly susceptible to oxidative damage, undergo membrane alterations, crenation, and hemolysis, contributing to anaemia. ROS also denatures hemoglobin, forming Heinz bodies and impairing oxygen-carrying capacity[22]. These changes, along with hyperglycemia-induced polyol pathway activation and sorbitol accumulation, exacerbate retinal ischemia, hypoxia, and the characteristic lesions of diabetic

retinopathy (microaneurysms, hemorrhages, exudates, neovascularisation, and macular edema) [23–26].

α -Tocopherol (vitamin E) is a potent lipid-soluble antioxidant that inhibits membrane lipid peroxidation, protects RBC integrity against hemolysis, and reduces retinal hypoxia [27–29]. Ascorbic acid (vitamin C) scavenges superoxide radicals, suppresses isoprostane formation, improves insulin sensitivity, reduces protein glycosylation and sorbitol accumulation, and enhances nitric oxide-mediated vasodilatation [30,31]. By mitigating oxidative stress and associated vascular events, early supplementation with vitamins C and E may arrest or reverse early signs of diabetic retinopathy [32–35]. The present study was conducted to evaluate the effect of vitamins C and E on insulin resistance, glycemic control, progression of diabetic retinopathy, and hemolytic anemia (using RBC morphology as a biomarker of oxidative stress) in a randomized, open-label, comparative pilot study.

Objectives of this study

Primary objective

To evaluate the efficacy of antioxidants (vitamin C and E) as add-on therapy in arresting the progression of diabetic retinopathy.

Secondary objectives

To evaluate morphological changes in red blood cells due to oxidative stress and their reversal with vitamins C and E; to assess improvement in hemoglobin and RBC count.

Materials and Methods

The study was conducted at the Regional Institute of Ophthalmology and

Government Ophthalmic Hospital, Egmore, Chennai, and the Institute of Diabetology, Rajiv Gandhi Government General Hospital, Chennai from June 2016-January 2017.

Study Design

Open-label, randomized, comparative pilot study with 60 patients (30 per group). Total duration per patient was 16 weeks (12 weeks intervention + 4 weeks post-treatment follow-up).

Inclusion Criteria

Patients of either sex aged 40-70 years, diagnosed with diabetic retinopathy (very mild to very severe NPDR), type-II diabetes mellitus for >5 years, on standard treatment, and willing to give informed consent.

Exclusion Criteria

Proliferative diabetic retinopathy, previous ocular surgery or injections, other ocular diseases, uncontrolled hypertension, renal or hepatic dysfunction.

Study Procedure

Out of 134 patients screened, 60 eligible patients with non-proliferative diabetic retinopathy (NPDR) were enrolled after obtaining written informed consent. Participants were randomised (1:1) using simple randomisation into two groups. The control group (n=30) received standard antidiabetic therapy (oral hypoglycemic agents and/or insulin). The study group (n=30) received standard antidiabetic therapy plus ascorbic acid (vitamin C) 500 mg and α -tocopherol (vitamin E) 400 mg twice daily for 12 weeks. Compliance was monitored using empty blister packs at 4-weekly follow-up visits (weeks 4, 8, and 12). After completion of the 12-week

intervention, all patients were followed up for an additional 4 weeks without study medication to assess the sustainability of effects on diabetic retinopathy grading and RBC morphology.

Assessments

Diabetic retinopathy grading (ETDRS scale), RBC morphology (% crenated RBCs with Heinz bodies), fasting blood glucose, hemoglobin, RBC count, and visual acuity at baseline, 4, 8, and 12 weeks.

Statistical Analysis

Data were analyzed using SPSS version 21. Within-group changes were assessed by paired t-test/Wilcoxon signed-rank test. Between-group comparisons used independent t-test/Mann-Whitney U test and ANCOVA. A p-value <0.05 was considered statistically significant.

Results

The mean duration of diabetes in the control group was 9.97 years and the study group was 10.07 years, which was statistically insignificant ($P=0.924$). There was no significant statistical difference between the groups. Intergroup analysis showed that both the groups were comparable at 0 weeks ($P=0.370$), but at the end of 12 weeks there was a greater reduction in fasting blood glucose level in the study group (176.60 to 105.77 mg/dL) compared to the control group (172.17 to 150.80 mg/dL) and this was found to be statistically significant ($P<0.001$). There

was no significant difference between the control and study group at 0 weeks ($P=0.253$), whereas, at the end of 12 weeks, the study group showed a significant decrease in the percentage of crenated RBCs ($P<0.001$).

The mean hemoglobin (Hb) was below average in both the control (11.25 gm/dl) and study group (10.8 gm/dl) at 0 weeks. After 12 weeks, the study group showed a significant increase in Hb (12.27gm/dL, $P<0.001$), while the control group did not show any significant difference (11.16 gm/dL, $P=0.228$). Between the groups, at 0 weeks there was no statistical difference ($P=0.138$) but at the end of 12 weeks, the study group showed a significant increase in hemoglobin than the control group ($P=0.001$). The mean total RBC count significantly increased in the study group from 3.94 million/ μ L at 0 weeks to 4.58 million/ μ L at 12 weeks ($P=<0.001$), while there was no statistically significant difference in the control group (0 weeks-4.02 million/ μ L, 12 weeks-4.01 million/ μ L, $P=0.491$).

The two groups were comparable at the beginning of the study ($P=0.393$). But at the end of the 12 weeks, the study group showed a significant increase in RBC count ($P=<0.001$). The morphology of RBCs before (crenated RBC) and after (normal RBC) is shown in Figure 1. The number of patients with the grading of diabetic retinopathy among study participants is depicted in Table 1.

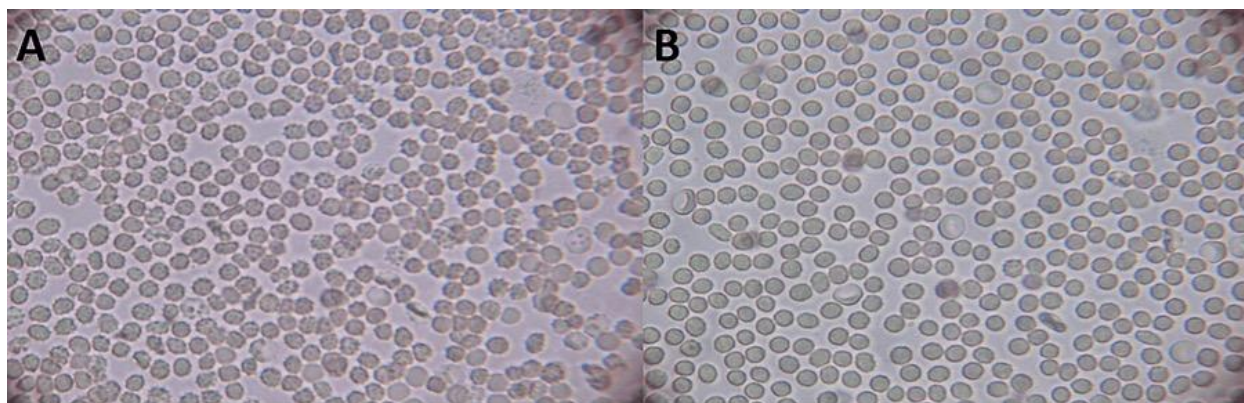


Figure 1. Morphology of RBCs, A-Before (crenated RBC), B-After (normal RBC)
RBC-Red blood cells

Table 1. Grading of diabetic retinopathy among study participants

Study population	Grading	0 week	At the end of 12 weeks	P-value
Control group (n=30)	Normal	0	0	0.09
	Very mild	0	1	
	Mild	3	0	
	Moderate	9	10	
	Severe	12	12	
	Very severe	6	7	
Study group (n=30)	Normal	0	1	0.001 (Significant)
	Very mild	0	13	
	Mild	0	14	
	Moderate	3	2	
	Severe	12	0	
	Very severe	15	0	
P-value		0.665	0.019 (Significant)	

Intergroup analysis at 12 weeks showed a statistically significant improvement in DR grading in the study group (p=0.019).

Visual status and complications among the study participants at the end of 12 weeks is shown in Tables 2 and 3

respectively. The fundus images of non-proliferative diabetic retinopathy are shown in Figure 2.

Table 2. Visual status among study participants at the end of 12 weeks

Visual acuity	Control group (n=30)	Study group (n=30)
	Number of patients (%)	Number of patients (%)
Improved \geq 6/12	1 (3.33%)	6 (20%)
Stable 6/18–6/36	20 (66.67%)	23 (76.67%)
Deterioration \leq 6/60	9 (26.67%)	1 (3.33%)

Table 3. Complications among the study participants

Adverse events	Control group (n=30)	Study group (n=30)	P-value
Nausea	3	1	-
Abdominal pain	1	1	-
Diarrhea	2	0	-
Hypoglycemia	2	1	-
Metallic taste	1	1	-
Incidence	30%	13%	0.209*

*P-value calculated using Fisher's Exact Test for overall incidence between groups. Individual event frequencies were too small for independent robust statistical comparison. The difference in overall incidence is not statistically significant ($p > 0.05$).

All events were mild. Beneficial effects on DR grading, visual acuity, and

RBC morphology were sustained during the 4-week post-treatment follow-up.

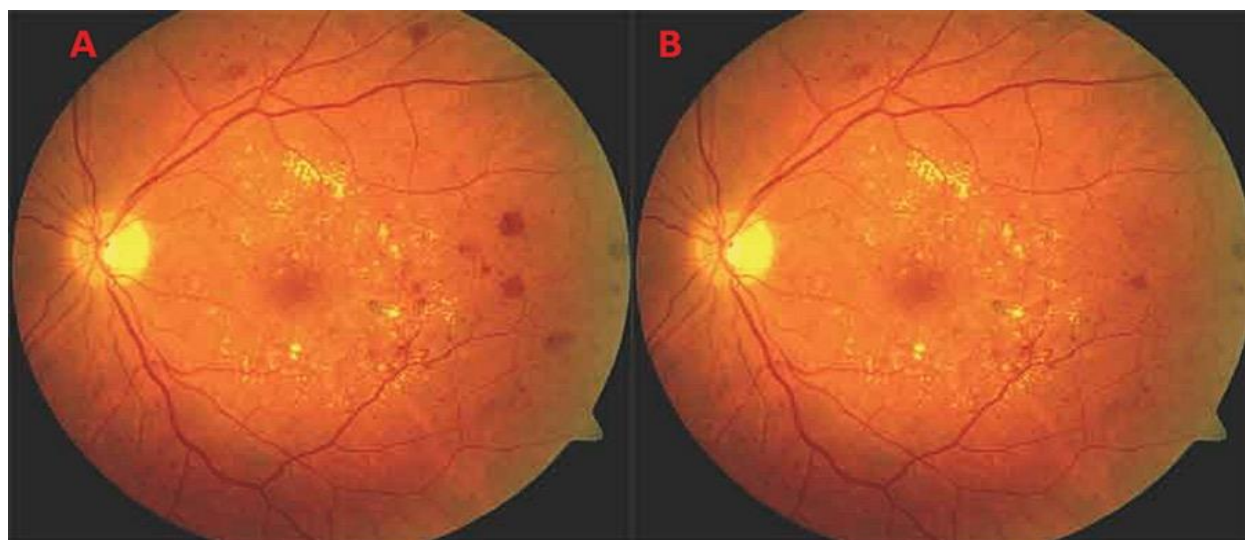


Figure 2. Fundus images showing non-proliferative diabetic retinopathy, A- Before treatment, B-After treatment

Discussion

Diabetic retinopathy is a microangiopathy characterized by microaneurysms, retinal hemorrhages, hard exudates, and cotton wool spots. Complications of proliferative diabetic retinopathy, including vitreous hemorrhage, neovascular glaucoma, and tractional retinal detachment, remain major causes of blindness [36]. Approximately 50% of diabetic patients develop retinopathy after 10 years and 90% after 30 years of disease onset [37].

In diabetes, hyperglycemia-driven excess free radical production coupled with antioxidant deficiency leads to oxidative tissue damage. Oxidative injury to RBC membranes results in crenated cells with loss of biconcave shape, while hemoglobin denaturation produces Heinz bodies [22]. These damaged RBCs undergo accelerated destruction in the spleen, causing hemolytic anemia [38,39]. Reactive oxygen species (ROS) also reduce nitric oxide bioavailability, promoting vasospasm [40], while lipid peroxidation of cell membranes

increases arachidonic acid and generates inflammatory isoprostanes [41]. Collectively, hemolytic anemia, vasospasm, and chronic inflammation contribute to retinal ischemia and progression of diabetic retinopathy[41].

The present study evaluated the efficacy of antioxidants α -tocopherol (vitamin E 400 mg) and ascorbic acid (vitamin C 500 mg) twice daily as add-on therapy to standard antidiabetic treatment in patients with non-proliferative diabetic retinopathy (NPDR) of more than five years duration. Sixty patients were randomized into control (standard therapy) and study groups (n=30 each) and followed for 12 weeks of treatment plus 4 weeks post-treatment.

Both groups had comparable baseline characteristics (mean age \approx 53 years, mean diabetes duration \approx 10 years). After 12 weeks, the study group showed significantly greater reduction in fasting blood glucose (176.60 to 105.77 mg/dL, $P<0.001$) compared to the control group (172.17 to 150.80 mg/dL, $P=0.025$), with intergroup difference $P<0.001$, indicating improved glycemic control with antioxidant supplementation.

Oxidative stress markers improved markedly in the study group. The percentage of crenated RBCs with Heinz bodies decreased dramatically from 80.40% to 7.20% ($P<0.001$), while no significant change occurred in the control group. Reticulocyte count fell from 2.50% to 0.40% ($P<0.001$) in the study group only. Hemoglobin rose from 10.8 to 12.27 g/dL ($P<0.001$) and total RBC count increased from 3.94 to 4.58 million/ μ L ($P<0.001$) in the study group, confirming that antioxidant therapy reduces free radical-induced RBC damage, hemolysis, and associated anemia [33,44].

Regarding retinopathy, ETDRS grading by fundus examination showed statistically significant regression in the number of patients with very severe, severe, and moderate NPDR in the study group ($P=0.001$) but not in the control group ($P=0.09$). Intergroup analysis confirmed greater reduction in retinopathy severity ($P=0.019$). Visual acuity improved in 20% of the study group versus 3.33% in the control group.

Antioxidants exert these benefits by scavenging ROS, preserving nitric oxide bioavailability to prevent vasospasm, reducing isoprostane-mediated inflammation, protecting RBC membrane integrity, and improving tissue oxygenation. Mild adverse effects (nausea, abdominal pain, diarrhea, hypoglycemia, metallic taste) were less frequent and less severe in the study group. Beneficial effects on glycemic control, RBC morphology, anemia, retinopathy grading, and visual acuity were sustained at the 4-week follow-up in the study group.

These findings are largely consistent with previous study reports on antioxidant therapy in diabetic retinopathy, although the magnitude and rapidity of improvement observed here appear more pronounced. Sanz-González et al. demonstrated that long-term supplementation with a multi-antioxidant formulation (including vitamins C and E) significantly slowed the progression of diabetic retinopathy over 60 months in patients with mild-to-moderate NPDR [34]. Similarly, Chatziralli et al. reported reduced oxidative stress markers and improved outcomes with vitamin E supplementation in insulin-dependent type 2 diabetes patients with retinopathy [29]. However, several other randomized controlled trials have demonstrated only

modest or inconsistent benefits on retinopathy progression with shorter durations or single-antioxidant regimens, while some studies found no significant structural improvement.

In conclusion, the addition of vitamins C and E to standard therapy resulted in superior glycemic control, normalization of RBC morphology, correction of hemolytic anemia, arrest/regression of NPDR, and better visual outcomes. These findings highlight the central role of oxidative stress in diabetic retinopathy and support RBC morphology as a simple, accessible biomarker of oxidative damage.

Limitations

Small sample size, short duration, open-label design. Larger, double-blind, randomized controlled trials with longer follow-up and inclusion of HbA1c and masked fundus photography grading are warranted.

Conclusions

Free radicals contribute significantly to the complications of diabetes. Antioxidants like α -tocopherol (vitamin E) and ascorbic acid (vitamin C) act as disease-modifying agents by reducing oxidative stress and insulin resistance. This pilot study demonstrates their potential in arresting diabetic retinopathy progression, normalizing RBC morphology, and improving quality of life in type-II diabetic patients.

Statements and Declarations

Conflicts of interest

The authors declare that they do not have conflict of interest.

Funding

No funding was received for conducting this study.

Competing Interests

The authors have no relevant financial or non-financial interests to disclose. The authors have no competing interests to declare that are relevant to the content of this article.

Ethics Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Institutional Ethics Committee approval was obtained (ECR/270/Inst./TN/2013/14051016). The study followed the Declaration of Helsinki and Good Clinical Practice (GCP) guidelines. Written informed consent was obtained from all individual participants included in the study.

Informed Consent

Informed consent was obtained from all individual participants included in the study. The authors affirm that human research participants provided informed consent for publication of the images in Figure 1 (RBC morphology) and Figure 2 (fundus images), where applicable.

Data Availability

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Authors' Contributions

LR: Conceptualization, Methodology, Investigation, Data Curation, Writing – Original Draft, Writing – Review & Editing, Visualization, Supervision, Project Administration. AS: Methodology, Formal Analysis, Investigation, Data Curation, Writing – Review & Editing. RK: Investigation, Resources, Writing – Review & Editing.

References

1. Khan MAB, Hashim MJ, King JK, Govender RD, Mustafa H, Al Kaabi J. Epidemiology of type 2 diabetes-global burden of disease and forecasted trends. *J Epidemiol Glob Health*. 2020;10(1):107-11. <https://doi.org/10.2991/jegh.k.191028.001>
2. World Health Organization. Diabetes. Geneva: WHO; 2023. Available from: <https://www.who.int/news-room/fact-sheets/detail/diabetes>
3. Centers for Disease Control and Prevention. Diabetes fast facts. Atlanta: CDC; 2023. Available from: <https://www.cdc.gov/diabetes/basics/quick-facts.html>
4. Pradeepa R, Mohan V. Epidemiology of type 2 diabetes in India. *Indian J Ophthalmol*. 2021;69(11):2932-8. https://doi.org/10.4103/ijo.IJO_1627_21
5. MedGenome. Diabetes is a growing burden in the society-latest scientific advances can help us manage it better. 2023. Available from: <https://diagnostics.medgenome.com/latest-scientific-advances-in-genetic-testing-can-help-us-manage-diabetes-better/>
6. Hiranjith GH. Diabetes is a growing burden but science has a solution. 2023. Available from: <http://health.economicstimes.indiatimes.com/health-files/diabetes-is-a-growing-burden-but-science-has-a-solution/1018>
7. Kropp M, Golubnitschaja O, Mazurakova A, et al. Diabetic retinopathy as the leading cause of blindness and early predictor of cascading complications—risks and mitigation. *EPMA J*. 2023;14(1):21-42. <https://doi.org/10.1007/s13167-023-00314-8>
8. Raman R, Vasconcelos JC, Rajalakshmi R, et al. Prevalence of diabetic retinopathy in India stratified by known and undiagnosed diabetes, urban-rural locations, and socioeconomic indices: results from the SMART India population-based cross-sectional screening study. *Lancet Glob Health*. 2022;10(12):e1764-73. [https://doi.org/10.1016/S2214-109X\(22\)00411-9](https://doi.org/10.1016/S2214-109X(22)00411-9)
9. Gale MJ, Scruggs BA, Flaxel CJ. Diabetic eye disease: a review of screening and management recommendations. *Clin Exp Ophthalmol*. 2021;49(2):128-45. <https://doi.org/10.1111/ceo.13894>
10. Lee R, Wong TY, Sabanayagam C. Epidemiology of diabetic retinopathy, diabetic macular edema and related vision loss. *Eye Vis (Lond)*. 2015;2:17. <https://doi.org/10.1186/s40662-015-0026-2>
11. Sharifi-Rad M, Anil Kumar NV, Zucca P, et al. Lifestyle, oxidative stress, and antioxidants: back and forth in the pathophysiology of

- chronic diseases. *Front Physiol.* 2020;11:694. <https://doi.org/10.3389/fphys.2020.00694>
12. Pizzino G, Irrera N, Cucinotta M, et al. Oxidative stress: harms and benefits for human health. *Oxid Med Cell Longev.* 2017;2017:8416763. <https://doi.org/10.1155/2017/8416763>
 13. Martemucci G, Costagliola C, Mariano M, D'Andrea L, Napolitano P, D'Alessandro AG. Free radical properties, source and targets, antioxidant consumption and health. *Oxygen.* 2022;2(1):48-78. <https://doi.org/10.3390/oxygen2020006>
 14. Phaniendra A, Jestadi DB, Periyasamy L. Free radicals: properties, sources, targets, and their implication in various diseases. *Indian J Clin Biochem.* 2015;30(1):11-26. <https://doi.org/10.1007/s12291-014-0446-0>
 15. Yu T, Robotham JL, Yoon Y. Increased production of reactive oxygen species in hyperglycemic conditions requires dynamic change of mitochondrial morphology. *Proc Natl Acad Sci U S A.* 2006;103(8):2653-8. <https://doi.org/10.1073/pnas.0511154103>
 16. Volpe CMO, Villar-Delfino PH, dos Anjos PMF, Nogueira-Machado JA. Cellular death, reactive oxygen species (ROS) and diabetic complications. *Cell Death Dis.* 2018;9(2):119. <https://doi.org/10.1038/s41419-017-0135-z>
 17. Hanna VS, Hafez EAA. Synopsis of arachidonic acid metabolism: a review. *J Adv Res.* 2018;11:23-32. <https://doi.org/10.1016/j.jare.2018.03.005>
 18. Hajeyah AA, Griffiths WJ, Wang Y, Finch AJ, O'Donnell VB. The biosynthesis of enzymatically oxidized lipids. *Front Endocrinol (Lausanne).* 2020;11:591819. <https://doi.org/10.3389/fendo.2020.591819>
 19. Sonnweber T, Pizzini A, Nairz M, Weiss G, Tancevski I. Arachidonic acid metabolites in cardiovascular and metabolic diseases. *Int J Mol Sci.* 2018;19(11):3285. <https://doi.org/10.3390/ijms19113285>
 20. Masenga SK, Kabwe LS, Chakulya M, Kirabo A. Mechanisms of oxidative stress in metabolic syndrome. *Int J Mol Sci.* 2023;24(17):7898. <https://doi.org/10.3390/ijms24097898>
 21. Sandoo A, van Zanten JJ, Metsios GS, Carroll D, Kitas GD. The endothelium and its role in regulating vascular tone. *Open Cardiovasc Med J.* 2010;4:302-12. <https://doi.org/10.2174/1874192401004010302>
 22. Herman TF, Javaid MU. Heinz body. In: *StatPearls.* Treasure Island (FL): StatPearls Publishing; 2023. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK441834/>
 23. Ruan Y, Jiang S, Musayeva A, Gericke A. Oxidative stress and vascular dysfunction in the retina: therapeutic strategies. *Antioxidants (Basel).* 2020;9(8):761. <https://doi.org/10.3390/antiox9080761>
 24. Safi SZ, Qvist R, Kumar S, Batumalaie K, Ismail ISB. Molecular mechanisms of diabetic retinopathy, general preventive strategies, and novel therapeutic targets. *Biomed*

- Res Int. 2014;2014:801269. <https://doi.org/10.1155/2014/801269>
25. Arévalo JF, Lasave AF, Zeballos DG, Bonafonte-Royo S. Diabetic retinopathy. In: Arévalo JF, editor. Retinal and choroidal manifestations of selected systemic diseases. New York: Springer; 2013. p. 273-89. https://doi.org/10.1007/978-1-4614-3646-1_21
 26. Kusuhara S, Fukushima Y, Ogura S, Inoue N, Uemura A. Pathophysiology of diabetic retinopathy: the old and the new. *Diabetes Metab J*. 2018;42(5):364-76. <https://doi.org/10.4093/dmj.2018.0182>
 27. Lauridsen C, Jensen SK. α -Tocopherol incorporation in mitochondria and microsomes upon supranutritional vitamin E supplementation. *Genes Nutr*. 2012;7(4):475-82. <https://doi.org/10.1007/s12263-012-0286-6>
 28. Antosik A, Czubak K, Cichon N, Nowak P, Zbikowska H. Vitamin E analogue protects red blood cells against storage-induced oxidative damage. *Transfus Med Hemother*. 2018;45(5):347-54. <https://doi.org/10.1159/000486605>
 29. Chatziralli IP, Theodossiadis G, Dimitriadis P, et al. The effect of vitamin E on oxidative stress indicated by serum malondialdehyde in insulin-dependent type 2 diabetes mellitus patients with retinopathy. *Open Ophthalmol J*. 2017;11:51-8. <https://doi.org/10.2174/1874364101711010051>
 30. Kaźmierczak-Barańska J, Boguszewska K, Adamus-Grabicka A, Karwowski BT. Two faces of vitamin C—antioxidative and pro-oxidative agent. *Nutrients*. 2020;12(5):1501. <https://doi.org/10.3390/nu12051501>
 31. Mason SA, Della Gatta PA, Snow RJ, Russell AP, Wadley GD. Ascorbic acid supplementation improves skeletal muscle oxidative stress and insulin sensitivity in people with type 2 diabetes: findings of a randomized controlled study. *Free Radic Biol Med*. 2016;93:227-38. <https://doi.org/10.1016/j.freeradbiomed.2016.01.006>
 32. Kowluru RA, Chan P-S. Oxidative stress and diabetic retinopathy. *Exp Diabetes Res*. 2007;2007:43603. <https://doi.org/10.1155/2007/43603>
 33. Matough FA, Budin SB, Hamid ZA, Alwahaibi N, Mohamed J. The role of oxidative stress and antioxidants in diabetic complications. *Sultan Qaboos Univ Med J*. 2012;12(1):5-18. <https://doi.org/10.12816/0003082>
 34. Sanz-González SM, García-Medina JJ, Zanón-Moreno V, et al. Clinical and molecular-genetic insights into the role of oxidative stress in diabetic retinopathy: antioxidant strategies and future avenues. *Antioxidants (Basel)*. 2020;9(11):1101. <https://doi.org/10.3390/antiox9111101>
 35. Kang Q, Yang C. Oxidative stress and diabetic retinopathy: molecular mechanisms, pathogenetic role and therapeutic implications. *Redox Biol*. 2020;37:101799. <https://doi.org/10.1016/j.redox.2020.101799>
 36. Kumar K, Baliga G, Babu N, et al. Clinical features and surgical outcomes of complications of proliferative diabetic retinopathy in young adults with type 1 diabetes mellitus versus type 2 diabetes mellitus—a comparative observational

- study. *Indian J Ophthalmol.* 2021;69(11):3289-95. https://doi.org/10.4103/ijo.IJO_1293_21
37. Khurana AK, Khurana B, Khurana AK. *Comprehensive ophthalmology.* 6th ed. New Delhi: Jaypee Brothers Medical Publishers; 2015.
38. Thiagarajan P, Parker CJ, Prchal JT. How do red blood cells die? *Front Physiol.* 2021;12:655393. <https://doi.org/10.3389/fphys.2021.655393>
39. Corrons JLV, Casafont LB, Frasnado EF. Concise review: how do red blood cells born, live, and die? *Ann Hematol.* 2021;100(11):2425-33. <https://doi.org/10.1007/s00277-021-04575-z>
40. Chen Q, Wang Q, Zhu J, Xiao Q, Zhang L. Reactive oxygen species: key regulators in vascular health and diseases. *Br J Pharmacol.* 2018;175(8):1279-92. <https://doi.org/10.1111/bph.13828>
41. Ito F, Sono Y, Ito T. Measurement and clinical significance of lipid peroxidation as a biomarker of oxidative stress: oxidative stress in diabetes, atherosclerosis, and chronic inflammation. *Antioxidants (Basel).* 2019;8(3):72. <https://doi.org/10.3390/antiox8030072>
42. Gelcho GN, Gari FS. Time to diabetic retinopathy and its risk factors among diabetes mellitus patients in Jimma University Medical Center, Jimma, Southwest Ethiopia. *Ethiop J Health Sci.* 2022;32(5):937-46. <https://doi.org/10.4314/ejhs.v32i5.9>
43. Ahmed RA, Khalil SN, Al-Qahtani MAA. Diabetic retinopathy and the associated risk factors in diabetes type 2 patients in Abha, Saudi Arabia. *J Family Community Med.* 2016;23(1):18-24. <https://doi.org/10.4103/2230-8229.172225>
44. Bajaj S, Khan A. Antioxidants and diabetes. *Indian J Endocrinol Metab.* 2012;16(Suppl 1):S267-71. <https://doi.org/10.4103/2230-8210.104057>