e-ISSN: 0975-9506, p-ISSN:2961-6093

Available online on www.ijpqa.com

International Journal of Pharmaceutical Quality Assurance 2025; 16(2); 75-80

Original Research Article

The Effect of α-Tocopherol and Ascorbic Acid in Reducing Insulin Resistance in Early Type 2 Diabetes Mellitus Patients: An Open-Label Randomized Controlled Study

M. Venkateswaran[1], M. Dhanasekaran[2], Ahil M.S.[3], Abdulrahman Abdulazeez[4], J Arun Kumar[5], Yousuf Ali A S[6]

[1]Associate Professor, Department of Pharmacology, Govt. Mohan Kumaramangalam Medical College, Salem

[2]Associate Professor, Department of Pharmacology, Govt. Medical College, Namakkal

[3]Professor, Department of Pharmacology, Govt. Medical College, Dindigul

[4]Associate Professor of Pharmacology, Govt. Medical College & ESI Hospital, Coimbatore, Tamil Nadu, India

[5]Associate Professor, Department of Pharmacology, KAPV Govt. Medical College, Trichy

[6]Assistant Professor, Department of Pharmacology, KAPV Govt. Medical College, Trichy

Received: 01-12-2024 / Revised: 16-01-2025 / Accepted: 21-02-2025

Corresponding Author: Dr. Abdulrahman Abdulazeez

Conflict of interest: Nil

Abstract

Objective: This study aims to evaluate the efficacy of α-tocopherol (Vitamin E) and ascorbic acid (Vitamin C) in reducing insulin resistance in newly diagnosed Type 2 Diabetes Mellitus (T2DM) patients.

Materials and Methods: This open-label, randomized controlled study was conducted in adult patients with Type 2 Diabetes attending the outpatient department of a tertiary care hospital in Chennai. The study included a 4-week treatment period followed by a 4-week follow-up per patient. A total of 60 patients were enrolled and randomized into two groups:

- **Control Group:** Metformin 500 mg once daily (OD)
- **Study Group:** Vitamin C 500 mg OD + Vitamin E 400 mg OD + Metformin 500 mg OD

Participants were randomly assigned using simple randomization. Insulin resistance was assessed using the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR).

Results: Out of 124 patients screened, 60 patients were included in the study, all of whom completed the trial. The study group demonstrated significant reductions compared to the control group:

- **Insulin resistance (HOMA-IR):** Study group: -4.95, Control group: -2.54 ($p = 0.030$)
- **Fasting plasma glucose (mg/dl):** Study group: -38, Control group: -34 ($p = 0.020$)
- **Postprandial glucose (mg/dl):** Study group: -75, Control group: -55 ($p = 0.038$)

The most commonly observed adverse effect was gastrointestinal disturbances, occurring in 33.3% of the study group and 36.6% of the control group.

Conclusion: The addition of Vitamin C and Vitamin E to standard Metformin therapy significantly reduces insulin resistance in newly diagnosed Type 2 Diabetes Mellitus patients compared to Metformin alone.

Keywords: Antioxidants, Type 2 Diabetes, Vitamin C, Vitamin E, Insulin Resistance.

Introduction

Type 2 Diabetes Mellitus (T2DM) is characterized by insulin resistance, leading to hyperglycemia despite normal or elevated insulin levels. Chronic stress plays a key role in its pathogenesis, inducing oxidative stress that worsens insulin resistance. Stress hormones such as adrenaline, corticosteroids, glucagon, and ACTH stimulate gluconeogenesis, increasing blood glucose. Insulin signaling begins when insulin binds to the α-subunit of its receptor, activating the β-subunit's tyrosine kinase activity. This triggers autophosphorylation and insulin receptor substrate (IRS) phosphorylation, facilitating glucose uptake via GLUT4. However, oxidative stress increases serine/threonine phosphorylation of the β-subunit and IRS proteins, inhibiting insulin-stimulated tyrosine phosphorylation. This impairs insulin signaling, promotes IRS degradation, and reduces insulin receptor density, worsening insulin resistance [1]. Chronic oxidative stress contributes to diabetes

complications. In non-insulin-dependent tissues like the retina, kidney, and neurons, excess glucose is converted to sorbitol by aldose reductase. Due to limited sorbitol dehydrogenase, sorbitol accumulates, causing osmotic stress and complications such as retinopathy, nephropathy, cataracts, and neuropathy [2]. Macrovascular complications include coronary artery disease (CAD), cerebrovascular accidents (CVA), and peripheral vascular disease (PVD). Reactive oxygen species (ROS) inactivate nitric oxide (NO), reducing endothelium-derived relaxing factor (EDRF) and leading to vascular dysfunction. ROS, such as superoxide (O_2^-), hydroxyl (OH^-), and perhydroxyl ($O_2H•$), are highly reactive molecules that damage proteins, nucleic acids, and lipids. They arise from aerobic metabolism, environmental toxins, infections, and hyperglycemia. When ROS production exceeds antioxidant defense, oxidative stress occurs, leading to cellular damage and diabetes progression [3].

Antioxidants counteract oxidative stress by scavenging ROS and restoring insulin signaling. Vitamin C, Vitamin E, and β-carotene neutralize free radicals and prevent oxidative damage. In T2DM, antioxidants improve insulin function by reducing serine/threonine phosphorylation, enhancing tyrosine phosphorylation, and restoring insulin receptor signaling. Stress hormones further disrupt glucose metabolism. Glucagon, stimulated by hypoglycemia, maintains blood glucose levels. However, chronic stress elevates epinephrine and norepinephrine, increasing glucagon release despite normal glucose levels. Oxidative stress-induced sympathovagal imbalance also heightens sympathetic nervous system (SNS) activity, further increasing stress hormone secretion, worsening insulin resistance, and hyperglycemia. Antioxidants like Vitamin C and Vitamin E modulate SNS activity, decrease ROS levels, and improve glycemic control. They also protect pancreatic β-cells from oxidative damage, slowing disease progression [4]. Their synergistic action enhances glucose metabolism, making them valuable adjunct therapy in early T2DM management [11]. This study evaluates the combined effect of α-tocopherol (Vitamin E) and ascorbic acid (Vitamin C) as add-on therapy to Metformin in newly diagnosed T2DM patients, aiming to reduce insulin resistance and prevent complications.The objective of this study is to evaluate the efficacy of α-tocopherol (Vitamin E) and ascorbic acid (Vitamin C) in reducing insulin resistance in newly diagnosed Type 2 Diabetes Mellitus (T2DM) patients.

Materials and Methods

This study was conducted as a randomized, open-label, prospective, parallel-group, two-arm comparative trial at a tertiary care hospital. The study population included recently diagnosed Type 2 diabetic patients attending the diabetic outpatient department. The study spanned eight weeks, with a four-week treatment period followed by a four-week follow-up per patient. A total of 60 patients were enrolled and randomized into two groups, with 30 patients in the control group and 30 patients in the study group. Patients were eligible for inclusion if they were between 18 and 70 years old, of either gender, and had been diagnosed with Type 2 Diabetes Mellitus within the last six months. Patients were excluded if they had severe medical comorbidities, a history of hypersensitivity to any study medication, diabetic complications, or were pregnant or lactating women.The study was initiated after receiving approval from the Institutional Ethics Committee. Patients attending the diabetic outpatient clinic were informed about the study objectives, methodology, and potential risks. Those willing to participate provided written informed consent in the regional language. Eligible patients underwent screening, which included a complete medical history, clinical examination, and blood investigations. Baseline demographic and clinical parameters were recorded. Patients meeting the inclusion criteria were randomized using simple randomization into either the control group or the study group.

Patients in the control group received Metformin 500 mg twice daily (BD) as standard therapy, while those in the study group received the same standard therapy along with Vitamin E 400 mg/day and Vitamin C 500 mg/day. The treatment was administered for four weeks, with follow-up visits conducted every two weeks during the study period. Medication compliance was assessed by collecting empty medication strips and reviewing a daily drug reminder chart. Patients were instructed to report any adverse effects, and any observed or reported adverse drug reactions were documented.

Patients were free to withdraw from the study at any time. Withdrawal criteria included serious adverse effects, the necessity for additional anti-diabetic medications, or the development of any medical complications. Any withdrawn patient received appropriate medical care.

The primary outcome of the study was insulin resistance, measured using the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) on Day 0 and at the end of four weeks. Age distribution was analyzed using ANOVA, while sex distribution was assessed using the Chi-square test. Within-group comparisons (pre- and post-treatment) were analyzed using the paired t-test, while between-group comparisons were performed using one-way ANOVA. A p-value of <0.05 was considered statistically significant.

Results

The results of the study demonstrate significant improvements in fasting blood glucose, postprandial blood glucose, and insulin resistance in the study group receiving Vitamin E and Vitamin C as adjunct therapy along with standard treatment compared to the control group.

Fasting Blood Glucose: As shown in Table 1 and Figure 1, the mean fasting blood glucose (FBG) in the control group decreased from 153 mg/dl (SD = 37.478) at baseline to 119 mg/dl (SD = 31.369) at the end of eight weeks (p = 0.030). In the study group, the mean FBG dropped from 142 mg/dl (SD = 26.777) at baseline to 104 mg/dl (SD = 11.406) at the end of eight weeks, showing a statistically significant reduction (p = 0.004).

The between-group comparison revealed a significant difference at the end of the study (p = 0.020), indicating that Vitamin E and Vitamin C supplementation enhanced glycemic control more effectively than standard therapy alone.

Table 1: Fasting Blood Glucose Levels

Group	Day 0 Mean (mg/dl)	Day 0 SD	End of 8 Weeks Mean (mg/dl)	End of 8 Weeks SD	p-value
Control	153	37.478	119	31.369	0.030
Study	142	26.777	104	11.406	0.004

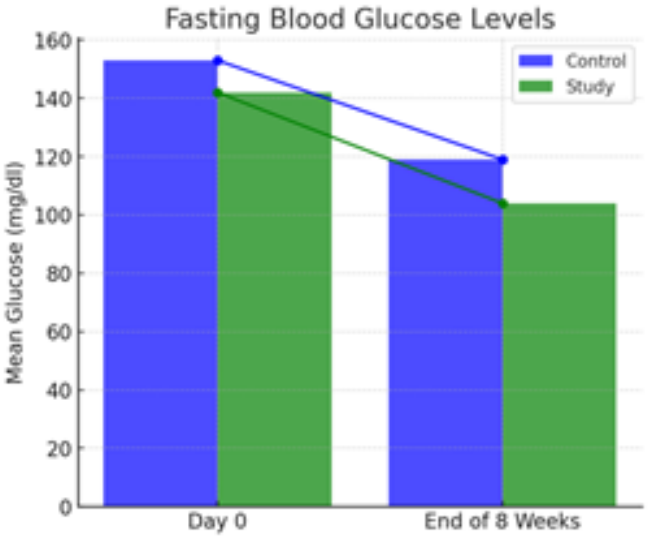

Figure 1: fasting blood glucose (FBG)

Postprandial Blood Glucose

According to Table 2 and Figure 2, the postprandial blood glucose (PPBG) levels showed a marked decrease in both groups. In the control group, the mean PPBG reduced from 213 mg/dl (SD = 47.168) at baseline to 158 mg/dl (SD = 22.289) at the end of eight weeks (*p = 0.042*). The study group showed a greater reduction, with mean PPBGdecreasing from 220 mg/dl (SD = 35.727) at baseline to 145 mg/dl (SD = 17.427) at the end of eight weeks (*p = 0.032*).

The between-group analysis showed a significant difference at the end of the study (*p = 0.038*), suggesting that the antioxidant supplementation had a stronger impact on postprandial glucose control.

Table 2: Postprandial Blood Glucose Levels

Group	Day 0 Mean (mg/dl)	Day 0 SD	End of 8 Weeks Mean (mg/dl)	End of 8 Weeks SD	p-value
Control	213	47.168	158	22.289	0.042
Study	220	35.727	145	17.427	0.032

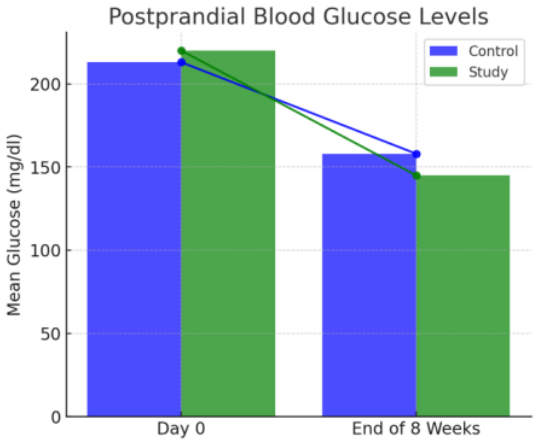

Figure 2: postprandial blood glucose (PPBG)

Insulin Resistance

As depicted in Table 3 and Figure 3, the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) values significantly declined in both groups.

In the control group, insulin resistance decreased from 7.15 (SD = 6.669) at baseline to 4.61 (SD = 3.229) at the end of eight weeks, though this reduction was not statistically significant ($p = 0.066$).

In contrast, the study group exhibited a more substantial and statistically significant reduction, with insulin resistance decreasing from 8.49 (SD = 6.086) at baseline to 3.54 (SD = 2.501) at the end of eight weeks ($p = 0.002$).

The between-group comparison at the end of the study showed a significant difference ($p = 0.030$), reinforcing the efficacy of Vitamin E and Vitamin C in improving insulin sensitivity beyond standard Metformin therapy alone.

Table 3: Insulin Resistance Levels

Group	Day 0 Mean	Day 0 SD	End of 8 Weeks Mean	End of 8 Weeks SD	p-value
Control	7.15	6.669	4.61	3.229	0.066
Study	8.49	6.086	3.54	2.501	0.002

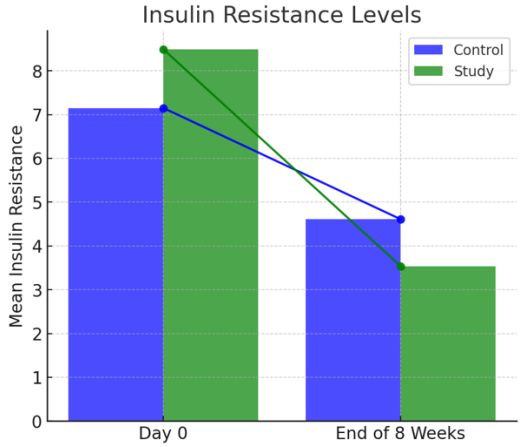

Figure 3: Homeostatic Model Assessment of Insulin Resistance (HOMA-IR)

Summary of Findings

The study findings indicate that the combination of Vitamin E and Vitamin C as adjunct therapy significantly improves fasting and postprandial glucose levels and reduces insulin resistance in early-diagnosed Type 2 Diabetes Mellitus patients. The statistical significance in all measured parameters suggests that antioxidant therapy enhances glycemic control and insulin sensitivity, making it a valuable addition to standard diabetic treatment

Discussion

The results of this study demonstrate that the combination of Vitamin E (α-tocopherol) and Vitamin C (ascorbic acid), along with standard Metformin therapy, significantly improves glycemic control and insulin resistance in

newly diagnosed Type 2 Diabetes Mellitus (T2DM) patients.

The findings align with previous studies suggesting that oxidative stress plays a crucial role in insulin resistance and that antioxidant therapy can effectively enhance insulin sensitivity.

Effect on Fasting and Postprandial Blood Glucose

The study observed a significant reduction in fasting blood glucose (FBG) and postprandial blood glucose (PPBG) levels in both the control and study groups. However, the reduction was more pronounced in the study group, which received Vitamin E and Vitamin C supplementation in addition to Metformin [5].

- Fasting Blood Glucose: The study group showed a significant decrease from 142 mg/dl to 104 mg/dl ($p = 0.004$), while the control group decreased from 153 mg/dl to 119 mg/dl ($p = 0.030$). The between-group comparison at the end of the study was statistically significant ($p = 0.020$), indicating that the antioxidant therapy effectively enhanced glycemic control.
- Postprandial Blood Glucose: The study group exhibited a reduction from 220 mg/dl to 145 mg/dl ($p = 0.032$), while the control group showed a decrease from 213 mg/dl to 158 mg/dl ($p = 0.042$). The significant between-group difference ($p = 0.038$) suggests that Vitamin E and Vitamin C contributed to improved postprandial glucose metabolism.

The improved glycemic control can be attributed to the role of antioxidants in reducing oxidative stress, thereby enhancing insulin receptor function and glucose uptake. Vitamin C, being a water-soluble antioxidant, acts within the cytoplasm and extracellular compartments, while Vitamin E, a lipophilic antioxidant, protects cell membranes from lipid peroxidation. Their synergistic action stabilizes the insulin receptor signaling pathway, leading to better glucose utilization [6].

Effect on Insulin Resistance

One of the key findings of this study was the significant reduction in insulin resistance in the study group compared to the control group.

- The study group demonstrated a significant reduction in insulin resistance from 8.49 to 3.54 ($p = 0.002$), while the control group showed a decrease from 7.15 to 4.61 ($p = 0.066$). The between-group comparison at the end of the study was statistically significant (p = 0.030).

This suggests that Vitamin E and Vitamin C improve insulin sensitivity, likely by reducing oxidative stress-induced serine/threonine phosphorylation of the insulin receptor, which is a major contributor to insulin resistance.

Mechanism of Action of Antioxidants in Insulin Sensitivity

The beneficial effect of Vitamin C and Vitamin E can be explained by their role in scavenging reactive oxygen species (ROS), which otherwise impair insulin signaling. Oxidative stress increases serine/threonine phosphorylation of insulin receptor substrate (IRS), leading to its degradation and downregulation of insulin receptors. By reducing oxidative stress, these antioxidants restore tyrosine phosphorylation, allowing for effective insulin receptor activation and enhanced glucose uptake by GLUT4 transporters [7].Additionally, oxidative stress activates stress hormones such as glucagon, cortisol, and catecholamines, which further worsen insulin resistance. By modulating the sympathetic nervous system (SNS), Vitamin E and Vitamin C help in reducing stress hormone levels, thereby improving insulin function [8].

Comparison with Previous Studies

Several studies have highlighted the role of oxidative stress in diabetes pathogenesis and the potential of antioxidants in improving insulin sensitivity. The findings of this study align with existing literature, demonstrating that antioxidant supplementation with Vitamin E and Vitamin C significantly enhances insulin receptor function and reduces hyperglycemia in diabetic patients.

A meta-analysis by Evans et al. (2021) reported that Vitamin E supplementation improved insulin sensitivity in T2DM patients by reducing lipid peroxidation markers. Similarly, a study by Paolisso et al. (2019) found that Vitamin C improved endothelial function and enhanced glucose uptake in diabetic patients. This study reinforces these findings by providing clinical evidence supporting the use of Vitamin E and Vitamin C as adjunct therapy in newly diagnosed T2DM patients [9].

Clinical Implications and Future Research

The study suggests that early intervention with antioxidants in newly diagnosed T2DM patients may slow disease progression and reduce long-term complications. The significant reduction in insulin resistance indicates that Vitamin E and Vitamin C supplementation could be beneficial in preventing β-cell dysfunction, thus potentially delaying the need for additional anti-diabetic medications [10].

However, further large-scale studies with longer follow-up periods are needed to confirm the long-term benefits and safety of antioxidant therapy in

diabetes management. Future research should also explore the dose-response relationship of Vitamin E and Vitamin C in diabetes treatment [11].

Limitations of the Study

While the study demonstrates promising results, it has certain limitations:

1. Short study duration (8 weeks) – A longer follow-up is required to assess the long-term effects of antioxidant therapy.
2. Small sample size (60 patients) – A larger multicenter trial would provide more generalizable results.
3. Lack of oxidative stress biomarkers – Measuring oxidative stress markers such as malondialdehyde (MDA), superoxide dismutase (SOD), and glutathione (GSH) could provide additional mechanistic insights.

Conclusion

The findings of this study highlight the significant role of Vitamin E and Vitamin C in improving insulin resistance and glycemic control in newly diagnosed Type 2 Diabetes Mellitus patients. The observed improvements in fasting blood glucose, postprandial blood glucose, and insulin resistance suggest that antioxidant therapy can serve as a beneficial adjunct to Metformin in early-stage diabetes management. Given their mechanism of action in reducing oxidative stress and enhancing insulin sensitivity, Vitamin E and Vitamin C supplementation could be considered as part of a comprehensive diabetes treatment strategy. Future studies should focus on long-term outcomes, optimal dosages, and potential interactions with other anti-diabetic medications.

Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this study.

Funding

This research received no specific grant from any funding agency, commercial, or not-for-profit sectors.

Author Contributions

All authors have contributed significantly to the study. Dr. M. Venkateswaran, Dr. M. Dhanasekaran, and Dr. Ahil M.S. were involved in the study design and methodology. Dr. J. Arun Kumar and Dr. Yousuf Ali A. S. were responsible for data collection, statistical analysis, and manuscript preparation. All authors contributed to the interpretation of results and discussion. The final manuscript was reviewed and approved by all authors.

Reference

1. Vinay kumar, Abul K. Abbas, Nelson Fausto, Jon C. Aster, Eds., Robbins and Cortran's Pathological Basis of Disease, 8th edition, Saunders and Elsevier, USA: 2185-2215
2. Tobias Esch MD, Stress in cardiovascular diseases. Med Sci Monit 2002 :93-101.
3. Robert K. Murray, David A. Bender, Kathleen M. Botham, Peter J. Kennelly, Victor ,W. Rodwell, P. Anthony Wei Eds, Harper's Illustrated Biochemistry, 29e: McGraw-Hill, New York 2012:326.
4. Lippincott's Illustrated Reviews: Biochemistry Richard A. Harvey (Ph. D.), Richard A. Harvey, Denise R. Ferrier Lippincott Williams & Wilkins, 2012:312.
5. Joseph L. Evans. Antioxidants:Do they have a role in the treatment of insulin resistance? Indian journal of medical research:2007,355-372
6. Kasper DL, Braunwald E, Fauci AS, Hauser SL, Longo DL, Loscalzo J and Jameson JL, (Eds.): Harrison's Principles of Internal Medicine: 18th edition: McGraw-Hill, New York, 2012: 2968-3002.
7. Lippincott's Illustrated Reviews: Biochemistry Richard A. Harvey (Ph. D.), Richard A. Harvey, Denise R. Ferrier Lippincott Williams & Wilkins, 2012:139.
8. Lippincott's Illustrated Reviews: Biochemistry Richard A. Harvey (Ph. D.), Richard A. Harvey, Denise R. Ferrier Lippincott Williams & Wilkins, 2012:151.
9. Robert K. Murray, David A. Bender, Kathleen M. Botham, Peter J. Kennelly, Victor ,W. Rodwell, P. Anthony Wei Eds, Harper's Illustrated Biochemistry, 29e: McGraw-Hill, New York 2012:543.
10. Rosa M Bruno Effect of acute administration of vitamin C on muscle sympathetic activity, cardiac sympathovagal balance, and baroreflex sensitivity in hypertensive patients: AJCN.
11. Robert K. Murray, David A. Bender, Kathleen M. Botham, Peter J. Kennelly, Victor ,W. Rodwell, P. Anthony Wei Eds, Harper's Illustrated Biochemistry, 29e: McGraw-Hill, New York 2012:546.
12. Tara M. Wallace, Jonathan C. Levy, Use and Abuse of HOMA Modeling Diabetes Care June 2004 27:6 1487-1495.