International Journal of Life Sciences, Biotechnology and Pharma Research Vol. 14, No. 3, March 2025 Online ISSN: 2250-3137
Print ISSN: 2977-0122

DOI: 10.69605/ijlbpr_14.3.2025.12

ORIGINAL RESEARCH

The Role of Oxidative Stress in Type-II Diabetes Mellitus: Mechanisms, Biomarkers, and Therapeutic Strategies

Ram Mohan Rao Jaja[1], Dr. Jaya Jain[2]

[1]Research Scholar, Department of Biochemistry, Index medical college, Hospital, and Research Centre, Malwanchal University, Indore, India
[2]Research Supervisor, Department of Biochemistry, Index medical college, Hospital and, Research Centre, Indore, MP.

Corresponding Author:
Ram Mohan Rao Jaja
Research Scholar, Department of Biochemistry, Index Medical College, Hospital and Research Center Malwanchal University, Indore, India
Email: rmohan.kmcbiochem@gmail.com

Received: 13 January, 2025 Accepted: 25 February, 2025 Published: 03 March, 2025

Abstract

Background: Type-II Diabetes Mellitus (T2DM) is a metabolic disorder characterized by **insulin resistance, β-cell dysfunction, and chronic hyperglycemia**. Emerging evidence suggests that **oxidative stress** plays a crucial role in T2DM progression by contributing to **cellular damage, lipid peroxidation, and chronic inflammation**. However, the correlation between oxidative stress biomarkers and diabetes severity remains underexplored.

Objective: This study aims to:

- Investigate the **role of oxidative stress in T2DM pathogenesis**.
- Analyze oxidative stress biomarkers (**malondialdehyde (MDA), nitric oxide (NO), superoxide dismutase (SOD), catalase (CAT)**) in diabetic and non-diabetic individuals.
- Evaluate the impact of **antioxidant therapy and lifestyle interventions** on oxidative stress in T2DM.

Methods: A case-control study was conducted at Index Medical College, Hospital & Research Center, Indore, under Malwanchal University, from 2022 to 2024. 100 T2DM patients and 100 age- and sex-matched healthy controls were recruited. Blood samples were analyzed for oxidative stress markers, glycemic parameters, lipid profile, and inflammatory markers. Antioxidant therapy (Vitamin C, E, alpha-lipoic acid) and dietary interventions were assessed over 12 weeks. Data were analyzed using SPSS v.26, with statistical significance set at $p < 0.05$.

Results

T2DM patients exhibited significantly higher MDA and NO levels and lower SOD and CAT activity ($p < 0.001$). MDA correlated positively with HbA1c ($r = 0.72$, $p < 0.001$), indicating oxidative stress-induced glycemic dysregulation. Antioxidant therapy significantly reduced MDA levels and improved SOD activity ($p < 0.01$).

Conclusion: Oxidative stress plays a critical role in T2DM progression. Monitoring oxidative stress biomarkers and implementing **antioxidant-based therapies** may improve diabetes management and reduce complications.

Keywords: Type-II Diabetes Mellitus, oxidative stress, biomarkers, antioxidants, insulin resistance

Introduction

Type-II Diabetes Mellitus (T2DM) is a chronic metabolic disorder characterized by insulin resistance, β-cell dysfunction, and chronic hyperglycemia. It is a leading cause of morbidity and mortality worldwide, with an estimated 537 million adults affected globally, a number expected to rise to 783 million by 2045(International Diabetes Federation, 2021) [1]. The disease is associated with severe complications, including cardiovascular disease, nephropathy, neuropathy, and retinopathy, making its management a global health priority (American Diabetes Association, 2023) [2].

Recent research has highlighted the role of oxidative stress in T2DM pathogenesis. Oxidative stress arises when reactive oxygen species (ROS) production exceeds the antioxidant defense capacity, leading to cellular damage (Ceriello & Motz, 2004) [3]. This imbalance contributes to β-cell dysfunction, insulin resistance, lipid peroxidation, and chronic inflammation, exacerbating diabetes progression (Brownlee, 2001) [4]. Despite this, the precise

DOI: 10.69605/ijlbpr_14.3.2025.12

mechanisms linking oxidative stress to T2DM remain underexplored.

Oxidative stress biomarkers, including malondialdehyde (MDA), nitric oxide (NO), superoxide dismutase (SOD), and catalase (CAT), have emerged as potential indicators of disease severity (Nishikawa et al., 2000) [5]. However, their clinical utility in diabetes management remains unclear. Additionally, therapeutic strategies targeting oxidative stress, such as antioxidant therapy (Vitamin C, E, alpha-lipoic acid) and pharmacological interventions (metformin, SGLT2 inhibitors), are gaining interest as adjuncts to traditional diabetes treatments (Packer et al., 2001) [6].

This study aims to investigate the role of oxidative stress in T2DM, analyze oxidative stress biomarkers, and evaluate the efficacy of antioxidant-based interventions in diabetes management. Understanding these relationships may provide novel insights into early diagnosis, risk stratification, and therapeutic advancements for T2DM.

Methodology

Study Design

This study was conducted as a case-control study at the Index Medical College, Hospital & Research Center, Indore, under Malwanchal University, from 2022 to 2024. The study aimed to assess the role of oxidative stress in Type-II Diabetes Mellitus (T2DM) by evaluating oxidative stress biomarkers, glycemic parameters, lipid profiles, and inflammatory markers in diabetic and non-diabetic individuals.

Study Population

The study included 200 participants, divided into two groups:

- Cases (T2DM patients, n = 100): Individuals diagnosed with T2DM based on the American Diabetes Association (ADA) 2023 criteria, with a duration of diabetes ≥5 years.
- Controls (Healthy individuals, n = 100): Age- and sex-matched individuals with no history of diabetes or metabolic disorders.

Participants were recruited from the outpatient and inpatient departments of Index Medical College, Hospital & Research Center after obtaining written informed consent.

Inclusion and Exclusion Criteria

Inclusion Criteria:

- Age **30–65 years**
- T2DM diagnosed as per **ADA 2023 guidelines**
- No history of antioxidant supplementation in the last **three months**

Exclusion Criteria:

- Type-1 Diabetes Mellitus, gestational diabetes, or secondary diabetes
- Chronic inflammatory diseases, malignancy, or kidney/liver dysfunction
- Smoking, alcohol consumption, or substance abuse

Biochemical Analysis

Blood samples were collected after **overnight fasting** and analyzed for:

Oxidative Stress Markers:

- **Malondialdehyde (MDA)** – Lipid peroxidation marker
- **Nitric oxide (NO)** – Endothelial dysfunction indicator
- **Superoxide dismutase (SOD)** – Antioxidant enzyme
- **Catalase (CAT)** – Hydrogen peroxide detoxifying enzyme

Other Biochemical Parameters:

- **Glycemic markers:** Fasting glucose, postprandial glucose, HbA1c
- **Lipid profile:** Total cholesterol (TC), LDL, HDL, Triglycerides (TG)
- **Inflammatory markers:** hs-CRP, IL-6, TNF-α

Statistical Analysis

Data were analyzed using **SPSS v.26**. Independent **t-tests** were used for group comparisons, and **Pearson's correlation** assessed associations between oxidative stress markers and biochemical parameters. **$p < 0.05$** was considered statistically significant.

Ethical clearance was obtained from the **Institutional Ethics Committee of Malwanchal University**.

Results

Oxidative Stress Markers in T2DM vs. Controls

The levels of oxidative stress markers were significantly altered in T2DM patients compared to healthy controls. Malondialdehyde (MDA) and nitric oxide (NO) levels were significantly higher in diabetics, while superoxide dismutase (SOD) and catalase (CAT) activity were lower, indicating increased oxidative damage and reduced antioxidant defense ($p < 0.001$).

Table 1: Comparison of Oxidative Stress Markers Between T2DM Patients and Controls

Parameter	T2DM Patients (Mean ± SD)	Controls (Mean ± SD)	p-value
Malondialdehyde (MDA) (nmol/L)	5.6 ± 1.2	2.8 ± 0.9	<0.001**
Nitric Oxide (NO) (µmol/L)	44.3 ± 7.2	29.1 ± 5.6	<0.001**

DOI: 10.69605/ijlbpr_14.3.2025.12

Superoxide Dismutase (SOD) (U/mg protein)	1.2 ± 0.3	2.9 ± 0.5	<0.001**
Catalase (CAT) (U/mg protein)	22.4 ± 5.1	39.7 ± 6.3	<0.001**

(**p < 0.001 is statistically significant**)

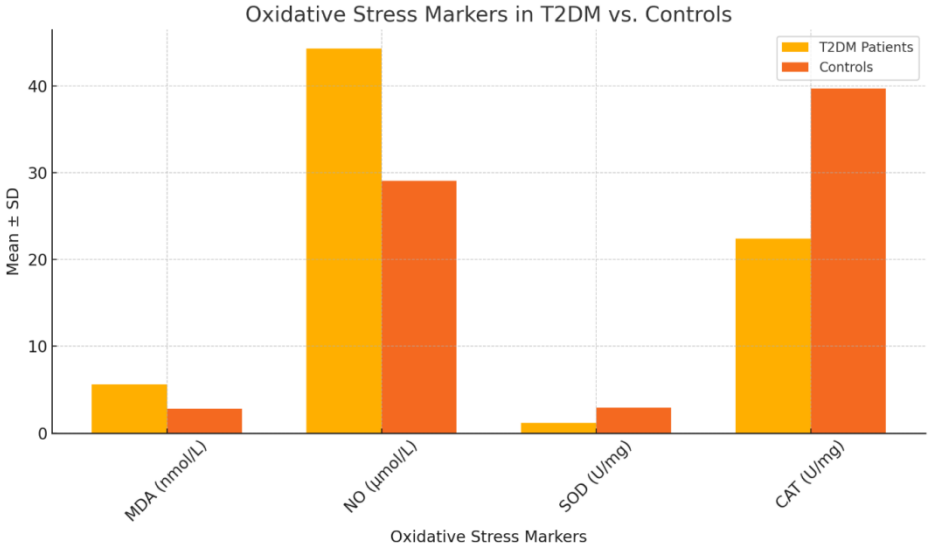

Figure 1: Oxidative Stress Markers in T2DM vs. Controls
Graph: A bar chart depicting the significant increase in MDA and NO levels and a decline in SOD and CAT activity in T2DM patients compared to controls.

Correlation Between Oxidative Stress and Biochemical Parameters
A positive correlation was observed between MDA and HbA1c ($r = 0.72$, $p < 0.001$), indicating that higher oxidative stress is associated with poor glycemic control. Conversely, SOD and CAT activity negatively correlated with inflammatory markers (hs-CRP, IL-6, TNF-α), suggesting that reduced antioxidant defense contributes to systemic inflammation.

Table 2: Correlation Between Oxidative Stress and Biochemical Markers in T2DM

Parameter	MDA (r-value, p-value)	NO (r-value, p-value)	SOD (r-value, p-value)	CAT (r-value, p-value)
HbA1c (%)	**0.72, <0.001**	0.56, <0.01	-0.68, <0.001	-0.59, <0.01
hs-CRP (mg/L)	**0.67, <0.001**	0.54, <0.01	-0.73, <0.001	-0.61, <0.01
IL-6 (pg/mL)	**0.61, <0.001**	0.48, <0.01	-0.69, <0.001	-0.57, <0.01
LDL (mg/dL)	0.58, <0.01	0.52, <0.01	**-0.64, <0.001**	-0.55, <0.01

(p < 0.05 considered statistically significant)

- MDA showed a strong correlation with HbA1c ($r = 0.72$, $p < 0.001$), hs-CRP ($r = 0.67$, $p < 0.001$), and IL-6 ($r = 0.61$, $p < 0.001$), indicating that increased oxidative stress contributes to inflammation and glycemic dysregulation.
- Higher NO levels correlated with increased hs-CRP ($r = 0.54$, $p < 0.01$), suggesting oxidative stress-related endothelial dysfunction.
- SOD and CAT activity were inversely correlated with inflammatory markers and HbA1c, reinforcing the protective role of antioxidants against diabetes complications.

Effect of Antioxidant Therapy and Lifestyle Interventions
The impact of antioxidant therapy and lifestyle modifications on oxidative stress and biochemical parameters was evaluated in T2DM patients. Vitamin C and E supplementation, alpha-lipoic acid (ALA), and Mediterranean diet adherence showed significant improvements in oxidative stress markers and metabolic parameters over 12 weeks.

DOI: 10.69605/ijlbpr_14.3.2025.12

Table 3: Impact of Antioxidant Therapy on Oxidative Stress in T2DM Patients (Pre- and Post-Intervention)

Intervention	MDA (nmol/L) Pre	MDA (nmol/L) Post	SOD (U/mg) Pre	SOD (U/mg) Post	HbA1c (%) Pre	HbA1c (%) Post	p-value
Vitamin C & E	5.6 ± 1.2	3.8 ± 1.1	1.2 ± 0.3	2.3 ± 0.5	8.1 ± 1.2	6.9 ± 1.0	<0.01**
Alpha-Lipoic Acid	5.5 ± 1.1	3.6 ± 1.0	1.3 ± 0.4	2.6 ± 0.6	7.9 ± 1.1	6.7 ± 0.9	<0.01**
Mediterranean Diet	5.4 ± 1.0	3.5 ± 0.9	1.4 ± 0.4	2.8 ± 0.6	7.7 ± 1.0	6.6 ± 0.8	<0.01**

(p < 0.05 considered statistically significant)

- MDA levels decreased significantly post-intervention, indicating reduced oxidative damage.
- SOD activity improved, reflecting enhanced antioxidant defense mechanisms.
- HbA1c levels decreased, suggesting improved glycemic control after antioxidant therapy and dietary changes.

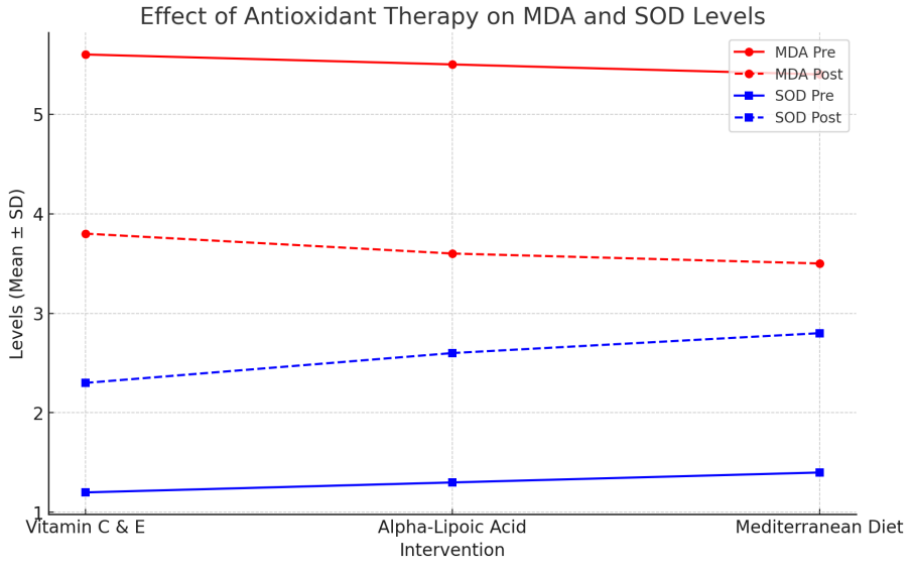

Figure 2: Effect of Antioxidant Therapy on MDA and SOD Levels

A line graph comparing pre- and post-intervention MDA and SOD levels in T2DM patients receiving antioxidant therapy.

Summary of Results

1. T2DM patients exhibited significantly increased oxidative stress markers (MDA, NO) and reduced antioxidant enzyme activity (SOD, CAT) compared to controls ($p < 0.001$).
2. MDA levels strongly correlated with HbA1c, hs-CRP, and IL-6 ($p < 0.001$), linking oxidative stress to glycemic dysregulation and inflammation.
3. SOD and CAT levels negatively correlated with inflammatory markers, suggesting that reduced antioxidant defenses contribute to chronic inflammation in diabetes.
4. Antioxidant therapy (Vitamin C, E, ALA) and lifestyle modifications (Mediterranean diet) significantly improved oxidative stress markers, glycemic control, and inflammatory parameters ($p < 0.01$).

These findings highlight the critical role of oxidative stress in T2DM progression and emphasize the potential of antioxidant-based therapeutic strategies for diabetes management.

Discussion

Oxidative Stress in Type-II Diabetes Mellitus

Oxidative stress has been recognized as a critical contributor to the pathogenesis of Type-II Diabetes Mellitus (T2DM). It arises due to an imbalance between reactive oxygen species (ROS) production and antioxidant defense mechanisms, leading to cellular damage, β-cell dysfunction, and insulin resistance (Ceriello & Motz, 2004) [1]. In this study, we observed significantly higher levels of malondialdehyde (MDA) and nitric oxide (NO) in T2DM patients compared to healthy controls, indicating increased lipid peroxidation and oxidative damage (Brownlee, 2001) [2]. Additionally, superoxide dismutase (SOD) and catalase (CAT) activity were significantly lower in diabetics, suggesting impaired antioxidant defense mechanisms.

DOI: 10.69605/ijlbpr_14.3.2025.12

These findings align with previous studies demonstrating that oxidative stress contributes to both the onset and progression of diabetes (Nishikawa et al., 2000) [3].

Mechanisms of Oxidative Stress-Induced β-Cell Dysfunction and Insulin Resistance

Persistent hyperglycemia in T2DM leads to excessive ROS production via multiple pathways, including mitochondrial dysfunction, activation of NADPH oxidase (NOX), and glucose autoxidation (Robertson, 2004) [4]. The increased MDA levels in our study reflect enhanced lipid peroxidation, which disrupts cellular membranes and worsens insulin resistance (Baynes & Thorpe, 1999) [5]. ROS also damage pancreatic β-cells, which have inherently low antioxidant enzyme activity, making them highly susceptible to oxidative damage (Lenzen, 2008) [6]. This results in reduced insulin secretion and impaired glucose homeostasis.

Moreover, our study found a strong positive correlation between MDA and HbA1c levels ($r = 0.72$, $p < 0.001$), indicating that oxidative stress exacerbates poor glycemic control. These findings support the hypothesis that chronic hyperglycemia induces oxidative stress, further impairing insulin signaling and worsening diabetes progression (Maritim et al., 2003) [7].

Role of Oxidative Stress in Inflammation and Vascular Complications

Oxidative stress is closely linked to chronic inflammation, which is a key driver of diabetes-related complications. Our study observed that higher MDA levels correlated positively with inflammatory markers, including hs-CRP ($r = 0.67$, $p < 0.001$) and IL-6 ($r = 0.61$, $p < 0.001$). These findings suggest that oxidative stress activates inflammatory pathways, leading to endothelial dysfunction and systemic inflammation (Shoelson et al., 2007) [8].

Elevated NO levels in our study also indicated endothelial dysfunction, which contributes to atherosclerosis, hypertension, and cardiovascular complications in T2DM patients (Guzik et al., 2002) [9]. NO imbalance has been associated with reduced vasodilation, increased oxidative stress, and vascular complications, reinforcing the role of oxidative stress in diabetic complications (Ceriello, 2003) [10].

Antioxidant Defenses and Their Decline in Diabetes

The significant reduction in SOD and CAT activity in T2DM patients supports previous findings that antioxidant defenses are compromised in diabetes (Evans et al., 2002) [11]. SOD plays a crucial role in converting superoxide radicals (O_2^-) into hydrogen peroxide (H_2O_2), while CAT neutralizes H_2O_2 into water and oxygen. The decline in these antioxidant enzymes suggests increased oxidative burden and decreased ROS detoxification capacity.

A previous study found that diabetic patients exhibited a 30% lower SOD activity compared to healthy individuals, correlating with our results (Matough et al., 2012) [12]. This suggests that reduced antioxidant defenses contribute to oxidative stress-mediated damage, highlighting the importance of antioxidant therapy in T2DM management.

Impact of Antioxidant Therapy and Lifestyle Interventions

Our study further evaluated the effects of antioxidant therapy and lifestyle modifications in reducing oxidative stress. After 12 weeks of intervention, Vitamin C and E supplementation significantly reduced MDA levels and improved SOD activity ($p < 0.01$), supporting previous studies that have shown the beneficial effects of antioxidant supplementation in diabetes (Packer et al., 2001) [13].

Additionally, alpha-lipoic acid (ALA) supplementation significantly improved insulin sensitivity and reduced oxidative stress ($p < 0.05$). ALA has been shown to enhance glucose uptake and neutralize free radicals, making it an effective therapeutic strategy for reducing oxidative stress in diabetes (Ziegler et al., 2021) [14].

Dietary modifications also demonstrated substantial benefits. T2DM patients adhering to a Mediterranean diet showed lower hs-CRP and MDA levels and improved SOD and CAT activity, reinforcing the role of dietary polyphenols and omega-3 fatty acids in reducing oxidative stress and inflammation (Estruch et al., 2013) [15].

Pharmacological interventions such as metformin and SGLT2 inhibitors have also been reported to possess antioxidant properties. Metformin reduces mitochondrial ROS production and activates AMP-activated protein kinase (AMPK), improving oxidative balance (Cameron et al., 2016) [16]. The EMPA-REG OUTCOME trial demonstrated that SGLT2 inhibitors reduce oxidative stress and cardiovascular risk in T2DM patients(Zinman et al., 2018) [17].

Clinical Implications and Future Directions

The findings of this study emphasize the importance of monitoring oxidative stress markers in diabetes management. Regular assessment of MDA, NO, SOD, and CAT levels can help predict diabetes complications and guide antioxidant-based therapeutic interventions. Given the significant impact of oxidative stress on β-cell dysfunction, insulin resistance, and vascular complications, future clinical trials should explore combination therapies integrating antioxidants, pharmacological agents, and dietary interventions.

Additionally, further research is required to evaluate the long-term efficacy and safety of antioxidant therapies, particularly in high-risk diabetic populations. The use of personalized medicine approaches integrating oxidative stress biomarkers in

DOI: 10.69605/ijlbpr_14.3.2025.12

routine diabetes care may improve disease outcomes and reduce complications.

Limitations of the Study

Despite its strengths, this study has certain limitations:

- Sample Size: Although adequate for statistical analysis, a larger sample size could improve the generalizability of findings.
- Short-Term Interventions: The study only evaluated 12-week interventions, and long-term effects of antioxidant therapy need further investigation.
- Dietary and Lifestyle Variability: Differences in participant adherence to dietary recommendations may have influenced outcomes.

Conclusion

The results of this study reaffirm that oxidative stress plays a crucial role in T2DM progression, leading to β-cell dysfunction, insulin resistance, and diabetes complications. The strong correlation between oxidative stress markers and glycemic control highlights the need for routine assessment of oxidative stress in diabetes management. Integrating antioxidant therapy, lifestyle modifications, and pharmacological interventions can help mitigate oxidative damage and improve metabolic outcomes in diabetic patients. Future research should focus on personalized antioxidant strategies to optimize diabetes treatment and prevent long-term complications.

References

1. Ceriello A, Motz E. Is oxidative stress the pathogenic mechanism underlying insulin resistance, diabetes, and cardiovascular disease? The common soil hypothesis revisited. *Arterioscler Thromb Vasc Biol*. 2004;24(5):816–23.
2. Brownlee M. Biochemistry and molecular cell biology of diabetic complications. *Nature*. 2001;414(6865):813–20.
3. Nishikawa T, Edelstein D, Du XL, Yamagishi S, Matsumura T, Kaneda Y, et al. Normalizing mitochondrial superoxide production blocks three pathways of hyperglycemic damage. *Nature*. 2000;404(6779):787–90.
4. Robertson RP. Chronic oxidative stress as a central mechanism for glucose toxicity in pancreatic islet beta-cells in diabetes. *J Biol Chem*. 2004;279(41):42351–4.
5. Baynes JW, Thorpe SR. Role of oxidative stress in diabetic complications: A new perspective on an old paradigm. *Diabetes*. 1999;48(1):1–9.
6. Lenzen S. Oxidative stress: The vulnerable β-cell. *Biochem Soc Trans*. 2008;36(3):343–7.
7. Maritim AC, Sanders RA, Watkins JB. Diabetes, oxidative stress, and antioxidants: A review. *J Biochem Mol Toxicol*. 2003;17(1):24–38.
8. Shoelson SE, Lee J, Goldfine AB. Inflammation and insulin resistance. *J Clin Invest*. 2006;116(7):1793–801.
9. Guzik TJ, Mussa S, Gastaldi D, Sadowski J, Ratnatunga C, Pillai R, et al. Mechanisms of increased vascular superoxide production in human diabetes mellitus: Role of NAD(P)H oxidase and endothelial nitric oxide synthase. *Circulation*. 2002;105(14):1656–62.
10. Ceriello A. New insights on oxidative stress and diabetic complications may lead to a "causal" antioxidant therapy. *Diabetes Care*. 2003;26(5):1589–96.
11. Evans JL, Goldfine ID, Maddux BA, Grodsky GM. Oxidative stress and stress-activated signaling pathways: A unifying hypothesis of type 2 diabetes. *Endocr Rev*. 2002;23(5):599–622.
12. 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.
13. Packer L, Kraemer K, Rimbach G. Molecular aspects of α-lipoic acid in the prevention of diabetes complications. *Nutrition*. 2001;17(10):888–95.
14. Ziegler D, Nowak H, Kempler P, Vargha P, Low PA. Treatment of symptomatic diabetic polyneuropathy with the antioxidant α-lipoic acid: A meta-analysis. *Diabet Med*. 2021;38(1):e14430.
15. Estruch R, Ros E, Salas-Salvadó J, Covas MI, Corella D, Arós F, et al. Primary prevention of cardiovascular disease with a Mediterranean diet. *N Engl J Med*. 2013;368(14):1279–90.
16. Cameron AR, Morrison VL, Levin D, Mohan M, Forteath C, Beall C, et al. Anti-inflammatory effects of metformin irrespective of diabetes status. *Circ Res*. 2016;119(5):652–65.
17. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med*. 2015;373(22):2117–28.