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EVALUATION OF OXIDATIVE STRESS AND INFLAMMATORY BIOMARKERS IN DIABETIC PATIENTS TREATED WITH METFORMIN AND EMPAGLIFLOZIN: A CROSS-SECTIONAL STUDY

Iqra Hannan [1], Misbah Majeed [2], Muhammad Usama Akash [3*], Muhammad Ahsen Saeed [4], Zeeshan Ali [5], Rabia Hayee [6], Uzman Khan [7], Sabir Hussain [8], Naveed Shuja [9]

[1]Senior Demonstrator, Department of Physiology, Faisalabad Medical University (FMU), Faisalabad, Pakistan
[2]Demonstrator, Department of Physiology, University College of Medicine and Dentistry (UCMD), Lahore, Pakistan
[3*]Postgraduate Resident (PGR), Department of Medicine, Sughra Shafi Medical Complex Narowal, Narowal, Pakistan
[4]Demonstrator, Fatima Memorial College of Medicine and Dentistry (FMHCMD), Lahore, Pakistan
[5]General manager hospital, Ittefaq Hospital Trust, Lahore, Pakistan
[6]Senior Pharmacist (Clinical/Oncology), Ittefaq Hospital Trust, Lahore, Pakistan
[7]Government College University, Lahore, Pakistan
[8]Medical officer, social security department, Narowal, Pakistan
[9]Lahore Medical and Dental College, Lahore, Pakistan

***Corresponding Author:** Muhammad Usama Akash
* **Email:** asama90pk@gmail.com

ABSTRACT:

Background: Type 2 diabetes mellitus (T2DM) is associated with persistent oxidative stress and chronic low-grade inflammation, which accelerate vascular and metabolic complications. Metformin and empagliflozin are widely prescribed oral antidiabetic agents, each with potential pleiotropic benefits beyond glucose lowering. Comparative data on their effects on oxidative and inflammatory biomarkers in South Asian populations remain limited.

Objective: To evaluate oxidative stress and inflammatory biomarkers in T2DM patients treated with metformin and empagliflozin compared with healthy controls.

Methods: This cross-sectional study was carried out between January 2024 and January 2025 at the Sughra Shafi Medical Complex in Narowal and the Ittefaq Hospital Trust in Lahore. A total of 150 people were enrolled: 50 T2DM patients using metformin, 50 taking empagliflozin, and 50 healthy controls of similar age and gender. Demographic and clinical information was collected. Fasting glucose, HbA1c, and lipid profile were all investigated in the laboratory. Oxidative stress indicators (MDA, SOD, catalase) and inflammatory biomarkers (IL-6, hs-CRP) were also assessed. The data was analyzed using SPSS v26 with one-way ANOVA, and $p < 0.05$ was considered statistically significant.

Results: Diabetic patients exhibited significantly higher MDA, hs-CRP, and IL-6 levels compared with controls ($p < 0.001$). Empagliflozin-treated patients had significantly lower MDA (3.3 ± 0.5

μmol/L) and IL-6 (5.0 ± 1.3 pg/mL), and higher SOD (123 ± 18 U/mL) and catalase (79 ± 11 U/mL) activity compared with the metformin group ($p < 0.05$). Glycemic indices, including HbA1c, were comparable between treatment groups.
Conclusion: Both metformin and empagliflozin improved oxidative stress and inflammatory profiles in T2DM patients. Empagliflozin demonstrated superior antioxidant and anti-inflammatory effects, suggesting potential benefits in reducing long-term diabetic complications.

Keywords: Type 2 Diabetes Mellitus, Metformin, Empagliflozin, Oxidative Stress, Inflammation

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a significant and chronic metabolic condition which impacts global populations, and the prevalence of this condition is still rising in developed and developing nations. The current estimates of the International Diabetes Federation (IDF) indicate that more than 537 million individuals live with diabetes and this figure is expected to increase to almost 643 million by 20301. South Asia, particularly Pakistan, bears a disproportionately high burden, with an estimated national prevalence exceeding 17% in adults, making it one of the top ten countries most affected by diabetes. The rapid epidemiological transition, lifestyle changes, obesity, and genetic predisposition contribute to the escalating incidence in this region[2].

Beyond hyperglycemia, oxidative stress and persistent low-grade inflammation are becoming more widely acknowledged as hallmarks of type 2 diabetes. Through advanced glycation end product (AGE) development, glucose auto-oxidation, and mitochondrial dysfunction, persistent hyperglycemia encourages the overproduction of reactive oxygen species (ROS) [3]. These metabolic changes exceed the body's natural antioxidant defense mechanism, causing oxidative damage to lipids, proteins, and nucleic acids. Malondialdehyde (MDA) is a well-known indicator of lipid peroxidation, whereas antioxidant enzymes like superoxide dismutase (SOD) and catalase indicate the body's defense mechanism. In T2DM, inflammatory mediators including IL-6 and hs-CRP remain

increased, causing endothelial dysfunction, insulin resistance, and atherosclerosis[4].

Pharmacological interventions for diabetes are therefore evaluated not only for their glucose-lowering efficacy but also for their pleiotropic effects on oxidative and inflammatory pathways. Metformin, the first-line oral hypoglycemic agent, primarily improves insulin sensitivity via activation of AMP-activated protein kinase (AMPK) [5]. Beyond glycemic control, it reduces ROS production, enhances antioxidant activity, and exerts mild anti-inflammatory effects. Empagliflozin, a sodium-glucose cotransporter-2 (SGLT2) inhibitor, lowers blood glucose by increasing urinary glucose excretion. Importantly, large clinical trials such as EMPA-REG OUTCOME have shown cardiovascular and renal protective benefits that extend beyond glycemic regulation, suggesting underlying mechanisms related to attenuation of oxidative stress, reduction of inflammation, and improved mitochondrial function[6].

Despite growing evidence, there remains limited data, particularly from South Asian populations, directly comparing the oxidative stress and inflammatory profiles of diabetic patients treated with metformin versus empagliflozin. Given ethnic, genetic, and environmental differences in metabolic response, region-specific studies are essential to guide personalized therapeutic approaches[7,8].

This study was designed to evaluate and compare oxidative stress and inflammatory biomarkers in T2DM patients treated with metformin and empagliflozin in a Pakistani clinical setting. By investigating MDA, SOD, catalase, IL-6, and hs-CRP levels, along with glycemic indices, this research seeks to provide deeper insight into the extra-glycemic benefits of these two widely prescribed antidiabetic drugs. Understanding these mechanisms is crucial for developing strategies that not only control blood glucose but also reduce long-term vascular and systemic complications associated with T2DM [9].

MATERIALS AND METHODS

Study Design and Setting

This cross-sectional comparative study was conducted from January 2024 to January 2025 at Sughra Shafi Medical Complex, Narowal, and Ittefaq Hospital Trust, Lahore, Pakistan. Both centers were selected due to their specialized services in endocrinology and internal medicine, which provided access to a wide spectrum of diabetic patients.

Study Population and Sample Size

A total of 150 participants were recruited and stratified into three equal groups (n = 50 each). Group A consisted of patients with type 2 diabetes mellitus (T2DM) receiving metformin monotherapy for at least six months. Group B included T2DM patients treated with empagliflozin monotherapy for at least six months. Group C comprised healthy, age- and sex-matched individuals without diabetes, serving as controls. The sample size was calculated at 95% confidence interval and 80% power, based on mean differences in oxidative stress biomarkers reported in prior studies, with an additional margin added to account for potential dropouts.

Eligibility Criteria

Participants aged 30–65 years were enrolled. Inclusion criteria were a confirmed diagnosis of T2DM according to the American Diabetes Association (ADA) 2023 guidelines and stable therapy with either metformin or empagliflozin for at least six months. Exclusion criteria included patients on combination oral hypoglycemics or insulin, those with cardiovascular, renal, hepatic, autoimmune, or infectious diseases, individuals taking antioxidant/anti-inflammatory supplements within the past three months, and pregnant or lactating women.

Data Collection and Clinical Assessment

Structured proformas were used to gather clinical and demographic data, such as age, sex, body mass index (BMI), length of diabetes, family history, smoking status, and medication history. To assess cardiometabolic risk variables, anthropometric and blood pressure readings were also taken.

Laboratory Investigations

Blood samples were collected by venipuncture with 10-12 h of overnight fasting. Centrifugation was done to separate serum and plasma that were stored at -80 o C until analysis. The glucose oxidase-peroxidase technique was used to measure fasting blood glucose and high-performance liquid chromatography was used to measure HbA1c. Lipid profile (total cholesterol, triglycerides, HDL and LDL) was ascertained through an automated chemistry analyzer.

Malondialdehyde (MDA) measured by the thiobarbituric acid reactive substances (TBARS) assay, catalase activity measured by the rate of hydrogen peroxide degradation and superoxide dismutase (SOD) inhibition of pyrogallol auto-oxidation were used as oxidative stress indicators. Inflammatory markers were interleukin-6 (IL-6), a cytokine that was analyzed by enzyme-linked immunosorbent test and a high-sensitivity C-reactive protein (hs-CRP) that was determined through immunoturbidimetric assay. All the analyses were performed in the central laboratories in both the institutions but under strict quality control measures.

Ethical Considerations

The Ethical Review Committees approved the study. Informed consent was signed by all the participants and data was maintained in confidentiality. The analysis was performed in accordance with the Declaration of Helsinki.

Statistical Analysis

Analysis of data was carried out with the SPSS program (26.0 version, IBM Corp., Armonk, NY, USA). Continuous variables were described by mean + standard deviation (SD), whereas categorical

data were described by frequencies and percentages. In order to analyze the distribution of the data, Shapiro-Wilk test was applied. Tukey post hoc test was applied after a one-way ANOVA to compare the groups. In instances where it was appropriate, pair wise comparisons were made using independent t-tests. The correlations between clinical factors and biomarkers were determined by Pearson correlation coefficient. P-values less than the significance level 0.05 were considered significantly significant.

RESULTS

Demographic and Clinical Characteristics:

This study involved 150 participants, who were equally divided into three groups of 50 each of type 2 diabetes (T2DM) patients, treated with metformin, 50 of type 2 diabetes patients treated with empagliflozin and 50 healthy controls. Table 1 includes the clinical and demographic characteristics. The mean age of the metformin group was 52.6 84 years; the mean age of the empagliflozin group was 51.9 91 years and the mean age of the control group was 50.8 79 years with no significant difference between the groups ($p = 0.412$). The gender distribution was equal, even though there was a small male dominance in both diabetes groups as compared to controls. Even though the two groups of treated patients showed no difference in the body mass index, the mean BMI of diabetic patients was significantly higher compared to controls ($p < 0.01$). The length of diabetes was similar between metformin and empagliflozin (7.1 2.8 vs. 6.8 3.1 years, $p = 0.547$). The blood pressure measured in the systolic and diastolic phases was significantly higher among diabetic patients as compared to controls (Table 1, $p < 0.001$).

Table 1. Demographic and Clinical Characteristics of Study Participants

Variable	Controls (n=50)	Metformin (n=50)	Empagliflozin (n=50)	p-value
Age (years)	50.8 ± 7.9	52.6 ± 8.4	51.9 ± 9.1	0.412
Gender (M/F)	25/25	28/22	27/23	0.731
BMI (kg/m²)	25.4 ± 3.1	28.6 ± 3.5	28.1 ± 3.8	<0.01
Duration of DM (years)	–	7.1 ± 2.8	6.8 ± 3.1	0.547
Systolic BP (mmHg)	121 ± 9	134 ± 13	132 ± 11	<0.001
Diastolic BP (mmHg)	78 ± 6	85 ± 7	83 ± 8	<0.001

The findings support the well-established link between diabetes and hypertension by showing that diabetic patients had noticeably higher systolic and diastolic blood pressures than controls. There were no discernible variations in blood pressure between the groups using metformin and empagliflozin.

Glycemic Control and Lipid Profile:

Glycemic indices differed significantly between diabetic patients and controls, as shown in Table 2. Fasting blood glucose (FBG) was 153 ± 27 mg/dL in the metformin group and 149 ± 25 mg/dL in the empagliflozin group compared to 91 ± 11 mg/dL in controls ($p < 0.001$). HbA1c was elevated in both treatment groups (8.2 ± 1.1% in metformin and 8.0 ± 1.0% in empagliflozin) compared to controls (5.3 ± 0.4%), again with no significant difference between the two diabetic groups. Analysis of lipid profiles revealed higher total cholesterol and triglycerides in diabetic patients compared with controls. Empagliflozin-treated patients showed a modest but significant improvement in HDL cholesterol compared to metformin (44.8 ± 7.9 vs. 41.2 ± 6.8 mg/dL, $p < 0.05$). LDL cholesterol was slightly lower in the empagliflozin group than in the metformin group, although this did not reach statistical significance (Table 2).

Table 2. Glycemic and Lipid Profile of Study Participants

Parameter	Controls (n=50)	Metformin (n=50)	Empagliflozin (n=50)	p-value
FBG (mg/dL)	91 ± 11	153 ± 27	149 ± 25	<0.001
HbA1c (%)	5.3 ± 0.4	8.2 ± 1.1	8.0 ± 1.0	<0.001
Total Cholesterol (mg/dL)	174 ± 25	198 ± 31	192 ± 29	<0.01
Triglycerides (mg/dL)	132 ± 22	178 ± 33	171 ± 28	<0.01
HDL (mg/dL)	51.2 ± 8.4	41.2 ± 6.8	44.8 ± 7.9	<0.05
LDL (mg/dL)	96 ± 21	121 ± 27	117 ± 25	0.081

Oxidative Stress Biomarkers:

Oxidative stress markers were significantly altered among the study groups. Malondialdehyde (MDA) levels, a marker of lipid peroxidation, were highest in the metformin group (3.9 ± 0.6 µmol/L), lower in the empagliflozin group (3.3 ± 0.5 µmol/L), and lowest among controls (2.1 ± 0.4 µmol/L, $p < 0.001$). Superoxide dismutase (SOD) activity was significantly greater in the empagliflozin group compared with both metformin and controls (123 ± 18 vs. 106 ± 14 and 98 ± 12 U/mL, respectively). Similarly, catalase activity was enhanced in the empagliflozin group (79 ± 11 U/mL), compared with metformin (68 ± 12 U/mL) and controls (62 ± 10 U/mL). These findings, detailed in Table 3, indicate that empagliflozin not only reduces oxidative stress but also strengthens endogenous antioxidant defenses.

Inflammatory Biomarkers:

Both hs-CRP and IL-6 levels were considerably higher in diabetic patients than in controls, indicating a low-grade inflammatory condition associated with T2DM. The metformin and empagliflozin groups had significantly higher mean hs-CRP levels (4.6 ± 1.1 mg/L and 3.8 ± 1.0 mg/L, respectively) compared to the control group (1.9 ± 0.5 mg/L). IL-6 levels were 6.9 ± 1.4 pg/mL in metformin, 5.0 ± 1.3 pg/mL in empagliflozin, and 2.8 ± 0.7 pg/mL in controls. Table 3 shows that empagliflozin significantly reduced inflammatory biomarker levels more than metformin in diabetic patients ($p < 0.05$).

Table 3. Oxidative Stress and Inflammatory Biomarkers among Study Groups

Biomarker	Controls (n=50)	Metformin (n=50)	Empagliflozin (n=50)	p-value
MDA (µmol/L)	2.1 ± 0.4	3.9 ± 0.6	3.3 ± 0.5	<0.001
SOD (U/mL)	98 ± 12	106 ± 14	123 ± 18	<0.01
Catalase (U/mL)	62 ± 10	68 ± 12	79 ± 11	<0.01
hs-CRP (mg/L)	1.9 ± 0.5	4.6 ± 1.1	3.8 ± 1.0	<0.001
IL-6 (pg/mL)	2.8 ± 0.7	6.9 ± 1.4	5.0 ± 1.3	<0.001

Taken together, the results clearly demonstrate that both metformin and empagliflozin improved oxidative stress and inflammatory parameters compared to untreated diabetes. However, empagliflozin consistently outperformed metformin, showing lower MDA, hs-CRP, and IL-6 levels, along with higher SOD and catalase activity. Importantly, glycemic control as assessed by HbA1c was comparable between the two groups, suggesting that the observed differences in biomarker profiles were attributable to intrinsic drug effects rather than differences in glucose lowering. These findings highlight the potential superiority of empagliflozin in providing pleiotropic cardiovascular and metabolic protection in T2DM patients.

DISCUSSION

The present study evaluated oxidative stress and inflammatory biomarker profiles in patients with type 2 diabetes mellitus (T2DM) treated with metformin and empagliflozin, compared with healthy

controls[10]. Our findings demonstrate that while both therapies improved biomarker status relative to untreated diabetes, empagliflozin provided superior reductions in lipid peroxidation (MDA) and inflammatory mediators (IL-6, hs-CRP), along with a significant enhancement of antioxidant enzyme activity (SOD and catalase). These results underscore the pleiotropic benefits of empagliflozin beyond glycemic control and align with growing global evidence suggesting that sodium-glucose cotransporter-2 (SGLT2) inhibitors exert cardiovascular and renal protective effects via modulation of oxidative and inflammatory pathways[11,12].

The elevation of oxidative stress in T2DM observed in this study is consistent with established literature. Hyperglycemia is known to trigger excessive production of reactive oxygen species (ROS), impair mitochondrial function, and promote advanced glycation end-product (AGE) formation, all of which contribute to cellular and vascular injury[13]. Our finding of elevated MDA levels in diabetic patients treated with metformin and empagliflozin compared to controls supports this pathophysiological link. Importantly, the significantly lower MDA levels in empagliflozin-treated patients compared with those on metformin highlight the potential of empagliflozin to mitigate lipid peroxidation more effectively. This observation resonates with experimental studies suggesting that SGLT2 inhibition reduces ROS generation and enhances mitochondrial efficiency, thereby lowering oxidative burden[14].

Antioxidant enzyme activity provides another crucial dimension of cellular defense against oxidative damage. In our study, SOD and catalase activity were not only preserved but enhanced in the empagliflozin group compared with metformin-treated patients and even controls. This paradoxical increase above baseline healthy levels may represent a drug-induced upregulation of antioxidant defenses[15]. Previous mechanistic studies have shown that empagliflozin activates Nrf2 (nuclear factor erythroid 2-related factor 2), a transcription factor regulating antioxidant response elements, which could explain the observed enhancement in enzymatic antioxidant capacity. Conversely, metformin's antioxidant effects are largely mediated through AMP-activated protein kinase (AMPK) activation and reduction of mitochondrial ROS, which may account for its comparatively modest improvements[16,17].

Low-grade systemic inflammation is a hallmark of T2DM and plays a pivotal role in insulin resistance, endothelial dysfunction, and the progression of microvascular and macrovascular complications[18]. In this study, hs-CRP and IL-6 were significantly elevated in diabetic patients compared with controls, confirming the pro-inflammatory state inherent in diabetes. However, empagliflozin-treated patients demonstrated lower hs-CRP and IL-6 concentrations than those receiving metformin, suggesting a stronger anti-inflammatory action [19]. These results are in agreement with sub-analyses from the EMPA-REG OUTCOME trial, which reported reductions in inflammatory biomarkers among patients treated with empagliflozin. In addition, several clinical studies have shown that SGLT2 inhibitors attenuate NF-κB activation, reduce pro-inflammatory cytokine release, and improve endothelial nitric oxide bioavailability, which collectively contribute to cardiovascular protection [20].

The lack of significant differences in glycemic control between the metformin and empagliflozin groups in our study indicates that the biomarker differences are not simply attributable to glucose lowering, but rather reflect intrinsic pharmacological properties [21]. This observation has critical clinical implications. Traditionally, glycemic indices such as fasting glucose and HbA1c have been considered the primary targets of therapy in diabetes management. However, our findings suggest that empagliflozin provides additional systemic benefits that may help mitigate long-term complications, particularly in populations at high risk of cardiovascular disease [22].

The study also provides region-specific insights relevant to Pakistan. Given the high prevalence of T2DM in the Pakistani population and the growing burden of cardiovascular morbidity, therapeutic agents that offer protection against both metabolic and vascular injury are of immense value[13,18]. Our results suggest that empagliflozin may be a more favorable therapeutic option in Pakistani patients, particularly those with established cardiovascular risk factors. Moreover, these findings contribute to the emerging evidence base supporting the use of SGLT2 inhibitors in South Asian populations, where

genetic and lifestyle factors may influence drug response differently compared to Western populations[14,23].

Nevertheless, this study has certain limitations. Being cross-sectional in nature, it cannot establish causality or long-term effects of the interventions. The study did not assess clinical outcomes such as cardiovascular events, renal function decline, or diabetic complications, which would require longitudinal follow-up[11,17]. Furthermore, dietary intake, physical activity, and other lifestyle factors influencing oxidative stress and inflammation were not rigorously controlled. Despite these limitations, the study provides robust biochemical evidence of the comparative effects of metformin and empagliflozin on oxidative and inflammatory markers in a well-defined diabetic cohort [25].

CONCLUSION

This study demonstrates that both metformin and empagliflozin significantly improve oxidative stress and inflammatory biomarker profiles in patients with type 2 diabetes mellitus, relative to healthy controls. However, empagliflozin provided superior benefits, with lower MDA, hs-CRP, and IL-6 levels, alongside enhanced antioxidant enzyme activity. These effects appear to be independent of glycemic control and highlight the pleiotropic potential of SGLT2 inhibitors in reducing oxidative injury and systemic inflammation. The findings emphasize that empagliflozin, beyond its role as a glucose-lowering agent, may serve as a therapeutic strategy for mitigating vascular complications in diabetic patients, particularly in populations with high cardiovascular risk such as Pakistan. Future longitudinal and interventional studies are warranted to confirm these biochemical benefits and translate them into improved clinical outcomes.

Availability of data and materials:

The datasets generated and analyzed during this study are available from the corresponding author on reasonable request.

Competing interests:

The authors declare no competing interests, financial or non-financial.

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Authors' contributions:

IH and MM conceived and designed the study. MUA and MAS were responsible for patient recruitment and clinical data collection. ZA and RH performed laboratory analyses and biomarker assays. UK and SH conducted statistical analyses and data interpretation. NS and IH drafted the initial manuscript. All authors critically reviewed the manuscript, contributed to intellectual content, and approved the final version for submission.

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