Original Article

Comparative Effects of Platelet-Rich Plasma and Erythropoietin on Oxidant/Antioxidant Balance in Diabetic Rats

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ABSTRACT

Diabetes is a chronic metabolic disease characterized by hyperglycemia, which leads to oxidative stress due to an imbalance between by oxidant and antioxidant. Platelet-Rich Plasma (PRP) has been used in clinical settings to stimulate tissue repair and cell proliferation in various medical fields. Erythropoietin (EPO) has demonstrated protective effects on various tissues and has mitigatied ischemia-reperfusion injury and promoting tissue regeneration. The aim of this study was to evaluate the effects of PRP and EPO on the oxidant/antioxidant balance in diabetic rats. A total of 30 male rats were divided into five groups: 1. Control; 2. Diabetic control, diabetes was induced using streptozotocin (STZ); 3. Diabetic + PRP: PRP was administered subcutaneously at 0.5 mL/kg twice a week for four weeks in diabetic rats; 4. Diabetic + EPO: EPO was administered at 300 units/kg three times a week for four weeks in diabetic rats; and 5. Diabetic + PRP + EPO: A combination of PRP and EPO was administered for four weeks. Diabetic rats showed significant reductions in superoxide dismutase (SOD), glutathione peroxidase (GPX), and glutathione (GSH) levels,as well as an increase in malondialdehyde (MDA) concentration, compared to the control group ($P < 0.05$). Compared to untreated diabetic rats, PRP and EPO treatments significantly increased SOD, GPX, and GSH quantities ($P < 0.05$) and lowered MDA concentrations. The combination therapy group exhibited the greatest improvements in antioxidant activities. This study demonstrates that both PRP and EPO both exhibit significant antioxidant effects in diabetic rats, and that the combined treatment shows the most pronounced improvement in oxidative stress markers. These results lay the groundwork for the clinical applications of PRP and EPO in enhancing antioxidant defenses and reducing oxidative damage in diabetic patients.

Keywords: Diabetes, Oxidative Stress, Platelet-Rich Plasma, Erythropoietin, Antioxidant Enzymes.

1. Introduction

Diabetes is a chronic metabolic disease characterized by lasting hyperglycemia caused by defects in insulin secretion or action. It poses a significant global health challenge (1). The disorder is primarily classified into two types: Type 1 and Type 2. Type 1 diabetes, which accounts for 5-10% of diabetes cases, results from impaired endocrine pancreatic β-cells, which generate a complete lack of insulin. Type 1 diabetes is caused by a combination of genetic predisposition and environmental factors (2). Type 2 diabetes, which is characterized by insulin resistance and is strongly associated with obesity, accounts for at least 90% of cases (3). Early detection and rigorous management of blood glucose levels, blood pressure, and cholesterol levels are crucial for preventing or delaying diabetes complications, which may include retinal damage to the retina, renal disorders, nerve damage, cardiovascular disorders, and increased mortality (4). Despite extensive research on the molecular mechanisms underlying diabetes complications, their exact pathophysiology remains incompletely understood (5, 6). A key factor in these complications is oxidative stress, which is caused by an imbalance between oxidant and antioxidant (7, 8). In diabetes, oxidative stress arises from multiple mechanisms, such as glucose autoxidation, formation of glycosylated proteins,and decreased levels of antioxidants including glutathione (GSH) and vitamin E, Additionally, glucose binds to antioxidant enzymes as superoxide dismutase (SOD) and catalase (CAT), impairing their detoxifying capabilities. Hyperglycemia can also increase NADPH oxidase activity and cytochrome P450 activity, causing increased ROS production. In Type 1 diabetes, Ketosis further exacerbates free radical generation (8, 9). Given the rising prevalence of diabetes and its extensive complications, there is a persistent need for innovative therapeutic approaches. Platelet-rich plasma (PRP) is a concentrated suspension rich in growth factors, including epidermal growth factor, insulin-like growth factor, vascular endothelial growth factor, nerve growth factor, and fibroblast growth factor (10). PRP has been used in clinical settings to stimulate tissue repair and cell proliferation in various medical fields, including dentistry, gynecology, urology, dermatology, and general surgery (11). PRP has also demonstrated potential in reducing oxidative stress in both in vivo and in vitro studies (12). However, its efficacy in improving pancreatic endocrine function in diabetes requires further investigation. Erythropoietin (EPO) is a hormone primarily produced by the kidneys in adults. It is a fundamental controller of erythropoiesis and is commonly used to treat anemia associated with chronic renal failure and chemotherapy (13, 14). Beyond hematopoiesis, EPO has demonstrated protective effects in various tissues and has moderated ischemia-reperfusion injury and promoting tissue regeneration (15). Latest studies propose that EPO may regulate glucose metabolism, potentially aiding in glucose homeostasis and mitigating diabetes complications (16, 17). EPO exerts antioxidant effects by enhancing intracellular antioxidants, and by reducing iron-induced oxidation. Additionally, the increase in red blood cell count induced by EPO decreases oxidative damage caused by the excessive antioxidant enzyme content of erythrocytes (18, 19). This study aims to compare the effects of PRP and EPO, as well as their combined administration, on oxidant/antioxidant parameters in diabetic rats. This study considers the significance of oxidative stress in diabetes pathophysiology and the potential therapeutic benefits of these treatments.

2. Materials and Methods

2.1. Animals

This studyutilized 30 male Wistar rats, each weighing approximately 200 ± 15 g,and was carried out in a in a controlled environment at 23 ± 2°C, with a humidity level of 24 ± 6%. Food and water were freely accessible to the rats. All The experimental procedures were approved by Shahid Chamran University of Ahvaz Laboratory Animal Care and Use Committee (Ethical code: EE/1401.2.24.226815/scu.ac.ir). The rats were randomly divided into five equal groupsof six rats each:

1. Control Group: Received 0.5 mL of normal saline subcutaneously (SC).

2. Diabetic Control Group: Received 65 mg/kg of streptozotocin (STZ) intraperitoneally (IP) to induce diabetes.

3. Diabetic PRP Group: After diabetes was induced, thevreceived 0.5 mL/kg of PRP, SC, twice a week for four weeks.

4. Diabetic EPO Group: After diabetes induction, received 300 units/kg of EPO, SC, three times a week for four weeks.

5. Diabetic EPO + PRP Group: After diabetes induction, received both EPO (300 units/kg) three times a week and PRP (0.5 mL/kg) twice a week, SC, for 4 weeks.

2.2. Diabetes Induction

Diabetes was induced using STZ at a dose of 65 mg/kg via the subcutaneous.SC. route. Blood glucose concentrations were tested using a glucometer72 hours after injection. Rats with blood glucose levels exceeding 250 mg/dL were confirmed as diabetic rats and included in the study (20).

2.3. PRP Preparation

PRP was prepared from an additional 20 male Wistar rats. Under anesthesia with ketamine/xylazine (50/10 mg/kg), whole blood was collected via cardiac puncture using sodium citrate as the anticoagulant. The blood was then centrifuged at 1000 rpm for 15 minutes to be separated into plasma (the upper layer), the buffy coat (the middle ,thin layer), and red blood cells (the lower layer). The upper and middle layers were transfered to a sterile tube and centrifuged again at 3000 rpm for five minutes. The upper two-thirds of the supernatant (platelet-poor plasma) was discarded, and the residual lower one-third was designated as PRP. The prepared PRP was stores at -70°C until use (21).

2.4. Sampling
Once the treatment period was complete, blood was sampled via cardiac puncture under ketamine/xylazine anesthesia. After centrifugation, theserum samples were stored at -70°C until laboratory analysis.

2.5. Oxidant/Antioxidant Analysis
Serum samples were analyzed for indicators of oxidant/antioxidant status . Superoxide dismutase (SOD) (Randox, Ransod, England) and glutathione peroxidase (GPX) (Randox, Ransel, England) activities were quantified spectrophotometrically using commercial kits following the manufacturer's instructions. Additionally, total antioxidant capacity (TAC), glutathione (GSH), and malondialdehyde (MDA) concentrations were evaluated using commercial reagents (Zellbio, Germany) according to the instructions on the kit. Statistical Analysis. The data was statistically analyzed using SPSS software. Normality was tested using the Shapiro-Wilk test. Means were compared using a one-way ANOVA followed by a Tukey's post-hoc test. The data are presented as the mean ± standard error (SE), and P<0.05 is considered statistically significant.

3. Results
3.1. SOD Activity
Serum activity of superoxide dismutase (SOD) enzyme showed a significant decline in the diabetic group compared to to the control group ($p<0.05$) (Table 1). Treatment with PRP, EPO, or a combination of the two significantly increased SOD activity compared to the untreated diabetic group ($p<0.05$). The greatest increase was observed in the group that received both EPO and PRP simultaneously.

3.2. GPX Activity
The serum activity of the glutathione peroxidase (GPX) enzyme decreased significantly in the diabetic rats compared to the control ones ($p<0.05$) (Table 1). Treatment with PRP, EPO, or their combination of the two significantly increased GPX activity compared to the untreated diabetic group ($p<0.05$). Groups that received EPO, either alone or in combination with PRP, demonstrated the GPX activity increases compared to the diabetic and control groups ($p<0.05$).

3.3. GSH Concentration
The serum concentration of reduced glutathione (GSH) followed a similar pattern as the other antioxidant enzymes. There was a significant reduction in the diabetic rats compared to the control ones ($p<0.05$), and a significant increase in the treated diabetic groups compared to the untreated diabetics ($p<0.05$) (Table 1). Groups receiving EPO, particularly the EPO and PRP combination , exhibited the greatest increases in GSH concentration compared to the other groups ($p<0.05$).

3.4. TAC
Despite slight variations, there were no significant differences in total antioxidant capacity (TAC) among the studied groups ($p>0.05$) (Table 1). Diabetics presented a slight increase in TAC, while the treated groups exhibited a minor decrease.

3.5. MDA Concentration
MDA levels were significantly higher in the diabetic rats and in the group receiving PRP than in the control group ($p<0.05$) (Table 1). EPO treatment and EPO combined with PRP treatment resulted in a significant decrease in MDA concentration compared to the diabetic rats ($p<0.05$).

4. Discussion
The global rise in diabetes prevalence and its related consequences necessitate exploring novel therapeutic approaches to alleviate the disease. Oxidative stress plays a central role in diabetes pathogenesis, necessitating interventions that can restore the oxidant/antioxidant balance (9, 22, 23). This study compared the effects of Platelet-Rich Plasma (PRP) and Erythropoietin (EPO) on this balance in diabetic rats. The current study observed significant reduction in the serum activity of superoxide dismutase (SOD) and glutathione peroxidase (GPX), as well as in glutathione (GSH) levels in the diabetic group.These results align with existing literature documenting decreased antioxidant defenses in diabetic conditions (24-26). This is primarily due to increased production of reactive oxygen species (ROS) and impaired antioxidant mechanisms.The elevated MDA levels in the diabetic group further support the presence of heightened oxidative stress as MDA is a well-established indicator of lipid peroxidation (27). Compared to the untreated diabetic group,PRP treatment significantly increased SOD, GPX, and GSH levels , indicating enhanced antioxidants activity. PRP is rich in numerous growth factors, including platelet-derived growth factor (PDGF), transforming growth factor-beta (TGF-β), and vascular endothelial growth factor (VEGF). These factors are known to stimulate tissue repair and renewal by stimulating cellular proliferation and angiogenesis (28, 29). Moreover, PRP has been revealed to have anti-inflammatory properties can mitigatemoderate oxidative stress by reducing the inflammatory responses

Table 1. Serum antioxidant and lipid peroxidation markers, as mean ± SE, in different treatment groups in diabetic rats.

	SOD (U/ml)	GPX (U/l)	GSH (µM)	TAC (µM)	MDA (µM)
Control	27.77 ± 1.28 a*	968.00 ± 40.61 a	309.14 ± 66.58 a	379.40 ± 5.93	44.58 ± 11.32 a
Diabetic	22.46 ± 0.27 b	805.53 ± 37.61 b	216.66 ± 96.73 b	395.77 ± 43.05	85.89 ± 15.45 b
PRP	28.88 ± 0.81 ac	901.60 ± 35.34 a	392.00 ± 39.80 a	343.40 ± 14.86	72.14 ± 1.49 b
EPO	31.18 ± 1.49 ac	1430.25 ± 353.14 c	538.00 ± 56.78 c	355.04 ± 21.44	52.49 ± 4.15 a
EPO+PRP	35.61 ± 5.05 c	2014.82 ± 212.44 c	696.66 ± 113.48 c	384.98 ± 18.88	49.22 ± 4.83 a

* Different lower-case letters in each column represent significant difference between groups ($p<0.05$).

that increase ROS production (30, 31). PRP's ability to enhance specific antioxidant enzymes may be attributed to its capacity to activate intracellular pathways that increase the expression of antioxidant genes. For instance, PRP activates the Nrf2 (nuclear factor erythroid 2-related factor 2) pathway, which is crucial for cellular defense against oxidative stress.This pathway induces induces the expression of several antioxidant enzymes, including SOD and GPX (32-34). Despite its significant effects on specific antioxidants, PRP treatment did not significantly alter the total antioxidant capacity (TAC). This suggests that, while PRP enhances specific antioxidant enzymes, its effect on overall antioxidant capacity may be limited or require a longer treatment durations or higher doses. EPO treatment, particularly when combined with PRP, produced the most substantial increases in SOD, GPX, and GSH levels in the serum of diabetic rats. This suggests a synergistic effect, as the combination therapy enhances the antioxidant defense system more effectively than either treatment alone. EPO's ability to modulate oxidative stress and enhance antioxidant defenses is well-established (33, 35, 36). EPO exerts its protective effects by binding to the erythropoietin receptor (EPOR) on target cells and activating multiple signaling pathways, including the PI3K/Akt and JAK2/STAT5 pathways. These pathways contribute to enhancing of antioxidant activities and inhibiting apoptosis in various cell types (36-38). In addition, EPO enhances the expression of heme oxygenase-1 (HO-1) and glutathione peroxidase, both of which are critical components of the cellular antioxidant defense (36). Furthermore, EPO treatment was associated with reduced lipid peroxidation, as evidenced by the decreased levels of MDA in our study.This indicates a reduction in oxidative damage to cell membranes. Interestingly, there were no significant differences inTAC among the studied groups. The slight increase in TAC in the diabetic group and the slight decrease in the treated groups suggest that TAC might not be as sensitive to diabetes-induced oxidative stress as the other measured parameters. This might be due to TAC’s complex nature, as it encompasses both enzymatic and non-enzymatic antioxidants (39). The antioxidant effects of PRP and EPO, especially when used in combination, highlight their potential therapeutic benefits in alleviating ROS formation and improving antioxidant defense in diabetic patients. Considering the role of oxidative stress in diabetes pathogenesis and development, as well asits consequences, these findings suggest that PRP and EPO could be valuable in developing new diabetes treatment strategies. Future studies should emphasize elucidating the underlying processes of PRP and EPO's effects on oxidative stress and exploring their long-term benefits and safety in clinical settings. Additionally, determining the optimal dosages and treatment durations to maximize therapeutic outcomes would be beneficial. In conclusion, this study demonstrates that both PRP and EPO exhibit significant antioxidant effects in diabetic rats, with the combined treatment showing the most pronounced improvements in oxidative stress markers. These results lay the groundwork for theclinical applications of PRP and EPO in enhancing antioxidant defenses and reducing oxidative damage in diabetic patients.

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Authors' Contribution
Study concept and design: S.M.J. and J.J. Acquisition of data: F.N. Analysis and interpretation of data: S.M.J. and A.R. Drafting of the manuscript: S.M.J. and F.N. Critical revision of the manuscript for important intellectual content: S.M.J. Statistical analysis: S.M.J. Administrative, technical, and material support: S.M.J., J.J. and A.R. Study supervision: S.M.J., J.J. and A.R.

Ethics
We hereby declare all ethical standards have been respected in preparation of the submitted article.

Conflict of Interest
The authors declare that they have no competing interests or personal relationships that could potentially influence the outcome of this research study.

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Data Availability
The data supporting the findings of this study are available upon request from the corresponding author.

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