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

Abstract

Diabetes is a persistent metabolic disease represented by hyperglycemia that leads to oxidative stress caused by oxidant/antioxidant imbalance. Platelet-Rich Plasma (PRP) has been utilized clinically to stimulate tissue repair and cell proliferation in various medical fields. Erythropoietin (EPO) has shown protective effects in various tissues, mitigating ischemia-reperfusion injury and promoting tissue regeneration. This study aimed to assess the effects of PRP and EPO on the oxidant/antioxidant balance in diabetic rats. A total of 30 male rats were assigned into five groups: 1. Control; 2. Diabetic control, diabetes induced using streptozotocin (STZ); 3. Diabetic + PRP: PRP was administered subcutaneously at 0.5 ml/kg two times 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 both PRP and EPO was administered for four weeks. Diabetic rats showed significant reductions in superoxide dismutase (SOD), glutathione peroxidase (GPX), and glutathion (GSH) levels and a rise in malondialdehyde (MDA) concentration in contrast to controls ($p<0.05$). PRP and EPO treatments significantly increased SOD, GPX, and GSH quantities ($p<0.05$) and lowered MDA concentrations compared to untreated diabetic rats. The combination therapy group exhibited the highest improvements in antioxidant activities. 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 provide a foundation for potential clinical

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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

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Introduction

Diabetes, a chronic metabolic disease described by lasting hyperglycemia caused by defects in insulin secretion or action, is posing a significant global health challenge (Banday et al., 2020). This disorder is primarily classified into two types: Type 1 and Type 2. Type 1 diabetes, accounting for 5-10% of diabetes cases, results from impairment of endocrine pancreatic β-cells, generating complete lack of insulin. The etiology of Type 1 diabetes comprises genetic predisposition and environmental factors (Katsarou et al., 2017). Type 2 diabetes, described by insulin resistance and strongly associated with obesity, constitutes at least 90% of diabetic patients (DeFronzo et al., 2015).

Early detection and rigorous management of blood glucose levels, blood pressure, and cholesterol are crucial in preventing or delaying diabetes complications, which can involve damage to the retina, renal disorders, nerve destruction, cardiovascular disorders, and increased mortality (Gregg et al., 2016). Despite extensive research on the molecular mechanisms underlying diabetes complications, their exact pathophysiology remains incompletely understood (Cole & Florez, 2020; Moghtadaei & Khani, 2021) A key factor in diabetes complications is oxidative stress, caused by an oxidant/antioxidant imbalance (Shahsavari et al., 2023; Asmat et al., 2016).

Oxidative stress in diabetes arises from multiple mechanisms, such as glucose autoxidation, formation of glycosylated proteins, decreased levels of antioxidants including glutathione (GSH) and vitamin E, and the binding of glucose to antioxidant enzymes as superoxide dismutase (SOD) and catalase (CAT), impairing their detoxifying capabilities. Additionally, hyperglycemia can increase NADPH oxidase activity, elevating cytochrome P450 activity, and causing intensified ROS production. Ketosis in Type 1 diabetes further exacerbates free radical generation (Yaribeygi et al., 2020; Asmat et al., 2016).

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, intense in growth factors including epidermal growth factor, insulin-like growth factor, vascular endothelial growth factor, nerve growth factor, and fibroblast growth factor (Qian et al., 2017). PRP has been utilized clinically to stimulate tissue repair and cell proliferation in various medical fields, including dentistry, gynecology, urology, dermatology, and general surgery (Marques et al., 2015). PRP has also demonstrated potential in reducing oxidative stress in both in vivo and in vitro studies (Elmongy et al., 2023; Soliman et al., 2019). However, its efficacy in improving pancreatic endocrine function in diabetes requires further investigation.

Erythropoietin (EPO), primarily produced by the kidneys in adults, is a fundamental controller of erythropoiesis and is commonly used to treat anemia associated with chronic renal failure and chemotherapy (Cernaro et al., 2019; Galli et al., 2015). Beyond hematopoiesis, EPO has shown protective effects in various tissues, moderating ischemia-reperfusion injury and promoting tissue regeneration (Peng et al., 2020). Latest studies propose that EPO may play a role in glucose metabolism regulation, potentially aiding in glucose homeostasis and mitigating diabetes

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complications (Niu et al., 2016; Maiese, 2015). 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 contributes to decreased oxidative damage caused by the excessive antioxidant enzyme content of erythrocytes (Zhang et al., 2022a; Osikov et al., 2015).

This study aims to compare the effects of PRP and EPO, as well as their combined administration, on oxidant/antioxidant parameters in diabetic rats, considering the significance of oxidative stress in diabetes pathophysiology and the potential therapeutic benefits of these treatments.

Materials and Methods

Animals

This study was carried out, utilizing 30 male Wistar rats, each weighing approximately 200 ± 15 g. Food and water were freely accessible to the rats and they were kept in a controlled environment at 23 ± 2°C, with a humidity level of 24 ± 6%. The experimental procedures were performed with the approval of 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 allocated into five equal groups, consisting of six rats each:

1. **Control Group:** Received 0.5 ml of normal saline, subcutaneously (SC).
2. **Diabetic Control Group:** Received streptozotocin (STZ) at a dose of 65 mg/kg intraperitoneally (IV) to induce diabetes.
3. **Diabetic PRP Group:** After diabetes induction, received 0.5 ml/kg of PRP, SC, twice a week for 4 weeks.

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

Diabetes Induction

Diabetes was induced using STZ at a dose of 65 mg/kg via SC route. Blood glucose concentrations were tested by means of a glucometer, 72 hours post-injection. Blood glucose levels exceeding 250 mg/dL were confirmed as diabetic rats and included in the study (Wang-Fischer and Garyantes, 2018).

PRP Preparation

PRP was prepared from 20 additional male Wistar rats. Under anesthesia with ketamine/xylazine (50/10 mg/kg), whole blood was collected via cardiac puncture utilizing sodium citrate as the anticoagulant. The blood was centrifuged at 1000 rpm for 15 minutes to be separated into plasma (upper layer), buffy coat (middle thin layer), and red blood cells (lower layer). The upper and middle layers were relocated to a sterile tube and centrifuged again at 3000 rpm for 5 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 preserved at -70°C until use (Zarin et al., 2019).

Sampling

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Once the treatment period was completed, blood sampling was done via cardiac puncture under ketamine/xylazine anesthesia. Following separation by centrifuging, serum samples were kept at -70°C until laboratory assessment.

Oxidant/Antioxidant Analysis

Serum samples were analyzed for oxidant/antioxidant status indicators. Superoxide dismutase (SOD) (Randox, Ransod, England) and glutathione peroxidase (GPX) (Randox, Ransel, England) activities were quantified spectrophotometrically using commertial kits following the manufacturer's instructions. Additionally, total antioxidant capacity (TAC), glutathione (GSH), and malondialdehyde (MDA) concentrations were evaluated using commercial reagents (Zellbio, Germany) in accordance with the kit instructions.

Statistical Analysis

Data was statistically analyzed by means of SPSS software. Normality was tested using the Shapiro-Wilk test. Means were compared via one-way ANOVA followed by Tukey's post-hoc test. Data was presented as mean ± standard error (SE), with $P<0.05$ assumed statistical significance.

Results

SOD Activity

Serum activity of superoxide dismutase (SOD) enzyme showed a significant decline in the diabetic group in comparison to the control group ($p<0.05$) (Table 1). Treatment with PRP, EPO, or their

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combination significantly increased SOD activity in contrast the untreated diabetic group ($p<0.05$), and the highest increase was observable in the group receiving both EPO and PRP simultaneously.

GPX Activity

Serum activity of glutathione peroxidase (GPX) enzyme was significantly decreased in the diabetic rats in contrast to the control ones ($p<0.05$) (Table 1). Treatment with PRP, EPO, or their combination significantly increased GPX activity in comparison to the untreated diabetic group ($p<0.05$). The groups which received EPO, either alone or in combination with PRP, showed the highest increases in GPX activity compared to both the diabetic and control groups ($p<0.05$).

GSH Concentration

Serum concentration of reduced glutathione (GSH) followed the similar pattern to the other antioxidant enzymes. There was a significant reduction in the diabetic rats contrasted to the control ones ($p<0.05$), and a significant increase in the treated diabetic groups in comparison to the untreated diabetics ($p<0.05$) (Table 1). The groups receiving EPO, particularly the combination of EPO and PRP, exhibited the highest increases in GSH concentration evaluated against the other groups ($p<0.05$).

TAC

Despite slight variations, there was not any significant difference in total antioxidant capacity (TAC) among the studied groups ($p>0.05$) (Table 1). The diabetics presented a slight increase in TAC, whereas the treated groups exhibited a minor decrease.

MDA Concentration

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MDA level was significantly increased in the diabetic rats and the group receiving PRP in comparison to the control group ($p<0.05$) (Table 1). EPO and the combination of EPO with PRP treatments resulted in a significant decrease in MDA concentration in comparison to the diabetic rats ($p<0.05$).

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 ($p<0.05$).

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Discussion

The global rise in diabetes prevalence and its related consequences necessitate the exploration of novel therapeutic approaches to alleviate the disease's consequences. Oxidative stress plays a central role in the pathogenesis of diabetes, requiring interventions that can restore the oxidant/antioxidant balance (Behmanesh et al., 2017; Caturano et al., 2023; Yaribeygi et al., 2020).

This experiment investigated the comparative outcomes of Platelet-Rich Plasma (PRP) and erythropoietin (EPO) on this balance in diabetic rats.

In the current study, the observed significant reduction in serum activity of superoxide dismutase (SOD) and glutathione peroxidase (GPX), as well as glutathione (GSH) levels in the diabetic group, aligns with existing literature documenting decreased antioxidant defenses in diabetic conditions (Eguchi et al., 2021; Darenskaya et al., 2021; Zhang et al., 2020). This is primarily due to intensified creation of reactive oxygen species (ROS) and impaired antioxidant mechanisms. Elevated MDA quantities in the diabetic group further support the presence of heightened oxidative stress, as MDA is a well-established indicator of lipid peroxidation (Elksnis et al., 2019).

PRP treatment significantly increased SOD, GPX, and GSH levels compared to the untreated diabetic group, indicating an enhancement of the antioxidants. PRP is rich in numerous growth factors comprising 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 (Sánchez et al., 2017; El- Sharkawy et al., 2007). Moreover, PRP has been revealed to have anti-inflammatory characteristics, which can further moderate oxidative stress by mitigating the inflammatory responses that exacerbate ROS generation (Bader et al., 2020; Rizwan et al., 2014).

PRP's ability to enhance specific antioxidant enzymes may be attributed to its capacity to activate intracellular paths that upregulate the expression of antioxidant genes. For instance, PRP can activate the Nrf2 (nuclear factor erythroid 2-related factor 2) pathway, which plays a pivotal role in cellular defense against oxidative stress by inducing the expression of several antioxidant enzymes, comprising SOD and GPX (Tognoloni et al., 2023; Zhang et al., 2022b; Martins et al.,

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2016). Despite its significant effects on specific antioxidants, PRP treatment did not significantly alter the total antioxidant capacity (TAC), suggesting that while PRP enhances specific antioxidant enzymes, its effect on overall antioxidant capacity may be limited or require a longer treatment duration 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, with the combination therapy enhancing the antioxidant defense system more effectively than either treatment alone. EPO's ability to modulate oxidative stress and enhance antioxidant defenses is well-established (Zhang et al., 2022b; Bailey et al., 2014; Katavetin et al., 2007). EPO exerts its protective effects by attaching to the erythropoietin receptor (EPOR) on target cells, activating multiple signaling pathways, including the PI3K/Akt and JAK2/STAT5 paths. These pathways contribute to the enhancement of antioxidant activities and the inhibition of apoptosis in various cell types (Maltaneri et al., 2024; Tanaka & Nangaku, 2012; Katavetin et al., 2007). In addition, EPO can enhance the expression of heme oxygenase-1 (HO-1) and glutathione peroxidase, both of which are critical components of the cellular antioxidant defense (Katavetin et al., 2007). Furthermore, EPO treatment was associated with reduced lipid peroxidation, as evidenced by decreased MDA levels in our study, indicating a reduction in oxidative damage to cell membranes.

Interestingly, TAC did not show significant differences 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 oxidative stress induced by diabetes as the other measured parameters. This might be due to the complex nature of TAC, which encompasses both enzymatic and non-enzymatic antioxidants (Rani & Mythili, 2014).

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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. Given the role of oxidative stress in the pathogenesis and development of diabetes and its consequences, these findings suggest that PRP and EPO could be valuable in developing new treatment strategies for diabetes management.

Forthcoming studies have to emphasis on 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, investigating the optimal dosages and treatment durations for maximizing 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 provide a foundation for potential clinical applications of PRP and EPO in enhancing antioxidant defenses and reducing oxidative damage in diabetic patients.

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Authors' Contribustion

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.

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.

Data Availability

The data that support the findings of this study are available on request from the corresponding author.

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اثرات مقایسه ای پلاسمای غنی از پلاکت و اریتروپویتین بر تعادل اکسیدان/آنتی اکسیدان در موش های صحرایی دیابتی

دیابت یک بیماری متابولیک پایدار است که با هیپرگلیسمی مشخص می شود که منجر به استرس اکسیداتیو ناشی از عدم تعادل اکسیدان/آنتی اکسیدان می شود. پلاسمای غنی از پلاکت (PRP) به صورت بالینی برای تحریک ترمیم بافت و تکثیر سلولی در زمینه های مختلف پزشکی استفاده شده است. اریتروپویتین (EPO) اثرات محافظتی در بافت‌های مختلف نشان داده است، آسیب‌های ایسکمی خونرسانی مجدد را کاهش می‌دهد و باعث بازسازی بافت می‌شود. این مطالعه با هدف بررسی اثرات پلاسمای غنی از پلاکت PRPو EPO بر تعادل اکسیدان/آنتی اکسیدان در موش‌های صحرایی دیابتی انجام شد. تعداد ۳۰ سر موش صحرایی نر در پنج گروه قرار گرفتند. ۱. کنترل، ۲. کنترل دیابت: ناشی از استرپتوزوتوسین (STZ)، ۳. دیابتی + PRP: PRP به صورت زیر جلدی با غلظت ۰/۵ میلی لیتر بر کیلوگرم دو بار در هفته به مدت چهار هفته در موش های صحرایی دیابتی تجویز شد. ۴. دیابتی + EPO: EPO با دوز ۳۰۰ واحد بر کیلوگرم سه بار در هفته به مدت چهار هفته در موش‌های دیابتی تجویز شد. و ۵. دیابتی + PRP + EPO: ترکیبی از هر دو PRP و EPO به مدت چهار هفته تجویز شد. موش‌های دیابتی کاهش معنی‌داری در سطوح سوپراکسید دیسموتاز(SOD) ، گلوتاتیون پراکسیداز (GPX) و گلوتاتیون (GSH) و افزایش غلظت مالون دی‌آلدئید (MDA) در مقایسه با گروه کنترل نشان دادند ($p<0.05$). تیمارهای PRP و EPO به طور معنی داری مقادیرSOD ، GPXو GSH را افزایش دادند ($p<0.05$) و غلظت MDA را در مقایسه با موش‌های دیابتی درمان نشده کاهش دادند. گروه درمان ترکیبی بالاترین افزایش را در فعالیت های آنتی اکسیدانی نشان داد. این مطالعه نشان می دهد که هر دو PRP و EPO اثرات آنتی اکسیدانی قابل توجهی را در موش های دیابتی نشان می دهند، در حالی که درمان ترکیبی برجسته ترین بهبود را در نشانگرهای استرس اکسیداتیو نشان می

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دهد. این نتایج پایه ای برای کاربردهای بالقوه بالینی PRP و EPO در تقویت دفاع آنتی اکسیدانی و کاهش آسیب اکسیداتیو در بیماران دیابتی فراهم می کند.

کلمات کلیدی: دیابت، استرس اکسیداتیو، پلاسمای غنی از پلاکت، اریتروپوئیتین، آنزیم های آنتی اکسیدان

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