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The effect of platelet-rich plasma (PRP) on blood glucose, inflammatory cytokines, and wound healing in diabetic rats

Maryam Babaei[1], Masoud Alirezaei[2], Moein Yazdkhasti[3*] and Ghasem farjanikish[4]

[1] DVM Graduated, Faculty of Veterinary Medicine, Lorestan University, Khorramabad, Iran
[2] Associate Professor, Department of Basic Sciences Faculty of Veterinary Medicine, Lorestan University, Khorramabad, Iran
[3] Assistant Professor, Department of Clinical Sciences, Faculty of Veterinary Medicine, Lorestan University, Khorramabad, Iran
[4] Associate Professor, Department of Pathobiology, Faculty of Veterinary Medicine, Lorestan University, Khorramabad, Iran

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Abstract

Diabetes mellitus is one of the most common metabolic disorders, characterized not only by persistent hyperglycemia but also by enhanced oxidative stress and inflammatory responses. Among proinflammatory cytokines, tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) play central roles in impairing insulin signaling, promoting lipolysis and gluconeogenesis, and exacerbating metabolic dysfunction. Platelet-rich plasma (PRP), enriched with growth factors and regulatory cytokines, has recently gained attention as a potential therapeutic strategy for tissue regeneration and inflammation control. In this study, diabetes was induced in Wistar rats using streptozotocin (65 mg/kg.), and full-thickness excisional wounds (2 cm) were created on the dorsum. The treatment group received daily topical applications of autologous PRP (50 U; 1 mL/kg body weight) from day 6 to day 20. Blood glucose was monitored at defined intervals, and serum IL-6 and TNF-α levels were measured using ELISA. PRP treatment significantly reduced blood glucose levels, particularly on days 3 and 21 of intervention. Moreover, TNF-α and IL-6, two pivotal cytokines involved in systemic inflammation, were markedly decreased in the PRP-treated diabetic group compared with untreated diabetic controls. The findings provide clear experimental evidence for the dual antihyperglycemic and anti-inflammatory properties of PRP in diabetes. By downregulating IL-6 and TNF-α, PRP not only improves glucose metabolism but also alleviates inflammatory responses, underscoring its potential as a novel adjunctive therapy for metabolic and inflammatory complications of diabetes

Key words: Diabetes mellitus, Inflammatory factors, glucose, PRP, Rat

Introduction

Diabetes mellitus is a group of physiological disorders that are characterized by increased blood sugar from insulin resistance, secretion, or glucagon excessive secretion. Type 1 diabetes (T1D) is an autoimmune disorder that leads to the destruction of panel beta cells. Type 2 (T2D), which is much more common, is primarily a progressive disorder of glucose regulation due to a combination of Malfunction in beta cells and insulin resistance (Blair, 2016).

Diabetes mellitus is a rapidly growing global health problem with profound social, health, and economic consequences. It is estimated that by 2045, approximately 700

* **Corresponding Author**: Moein Yazdkhasti, Assistant Professor, Department of Clinical Sciences, Faculty of Veterinary Medicine, Lorestan University, Khorramabad, Iran
E-mail: yazdkhasti.m@lu.ac.ir

million people will be living with the disease worldwide (Kaul et al, 2013). Population aging and obesity are considered two major drivers of this increase. Furthermore, studies indicate that up to 50% of individuals with diabetes may remain undiagnosed for as long as 10 years after disease onset, suggesting that the true prevalence of diabetes is likely considerably higher than current estimates (Kaul et al, 2013).

Plasma is the liquid component of blood that primarily contains water and proteins. In addition, it carries platelets and coagulation factors, which play essential roles in blood clotting and tissue repair. Platelet-rich plasma, also known as PRP, is an autologous biological product used in medicine as a treatment for tissue repair. PRP has been of great value as a treatment due to its easy preparation, low-cost processing, and its autologous nature. During tissue damage, these platelets are activated and growth factors such as platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), release epidermal growth factor (EGF) and others, thereby adhere to the site of injury (Kucuk et al, 2014).

Today, research has been done on the impact of PRP on wound healing and tendon rupture and has explained positive results in this area (Arnoczky et al, 2011).

PRP has been shown to accelerate epidermal reconstruction, stimulate epithelial and endothelial cell proliferation, enhance collagen synthesis, promote angiogenesis, and improve soft tissue healing. In addition, PRP can counteract impaired wound healing induced by glucocorticoids. Owing to its autologous origin, PRP has minimal risk of infection and is widely applied in diverse clinical fields, including head and neck surgery, cardiovascular surgery, oral and maxillofacial surgery, burn and wound management, and periodontics. Although a large number of studies have investigated the therapeutic potential of PRP, further evidence is still required regarding its systemic effects, particularly in the context of diabetes (Agale, 2013; Marx, 2004).

Interleukin-6 (IL-6) is a pleiotropic cytokine that plays a dual role in inflammation and tissue repair. On the one hand, IL-6 is considered a pro-inflammatory mediator involved in the acute inflammatory response; on the other hand, transient increases in IL-6 are essential for initiating angiogenesis, fibroblast migration, collagen deposition, and subsequent tissue remodeling during wound healing. Therefore, the biological impact of IL-6 depends largely on its temporal and spatial expression (Lin ZQ, 2020).

The present study was therefore designed to evaluate the effect of PRP on blood glucose levels and inflammatory markers (IL-6 and TNF-α) in an experimental diabetic rat model, providing insights into both local wound healing and systemic metabolic regulation.

Materials and Methods

Animals

In this experimental study, 24 adult male Wistar rats weighing 200 ± 10 g were obtained from the Razi Research Center, Lorestan University of Medical Sciences (Iran). Animals were maintained under standard laboratory conditions (12 h light/dark cycle, temperature 25 ± 2 °C, relative humidity 40–60%) with free access to standard chow and water. All experimental procedures were carried out in accordance with institutional guidelines and ethical standards for the care and use of laboratory animals. Rats were randomly assigned to three groups (n = 8 per group): Control, Diabetic, and Diabetic + PRP (Isbary et al, 2010).

Diabetes Induction

Diabetes was induced by a single intraperitoneal injection of streptozotocin (STZ, 65 mg/kg; Sigma-Aldrich, USA) freshly dissolved in citrate buffer (pH 4.5). Seventy-two hours post-injection, blood glucose levels were measured using a glucometer (Accu-Chek, Germany). Rats with fasting blood glucose levels above 250 mg/dl were considered diabetic. Animals in the control group received an equal volume of citrate buffer (Wszola et al., 2021).

PRP Preparation

Autologous platelet-rich plasma (PRP) was prepared from donor rats using a two-step centrifugation protocol. Briefly, whole blood was collected into tubes containing sodium citrate-dextrose as an anticoagulant. The first centrifugation was performed at 1700 rpm for 10 minutes, and the plasma supernatant was transferred to a fresh tube. A second centrifugation was then carried out at 3000 rpm for 10 minutes. Approximately two-thirds of the upper plasma fraction was discarded, and the remaining one-third containing the platelet pellet was designated as PRP. The PRP was freshly prepared and used for topical wound application.

Wound Creation and Treatment

Animals were anesthetized with an intraperitoneal injection of ketamine (70 mg/kg) and xylazine (10 mg/kg). The dorsal hair was shaved, and the skin was disinfected with povidone-iodine. Using sterile scissors and forceps, a 2 cm diameter full-thickness excisional wound was created on the dorsum of each rat. In the treatment group (Diabetic + PRP), 50 units of autologous PRP were applied topically to the wound site once daily from day 6 post-wounding for two weeks (until day 20).

Blood Glucose and Cytokine Measurement

Blood glucose levels were monitored in diabetic animals on days 0 (wound creation), 3, 12, and 21 using a glucometer (Accu-Chek, Germany). On day 21, blood samples were collected, and serum levels of pro-inflammatory cytokines (IL-1β, IL-6, TNF-α) were measured using rat-specific ELISA kits (Karmania Pars Gene, Iran) according to the manufacturer's instructions.

Statistical analyses

Statistical analyses were performed using GraphPad Prism. Data are expressed as mean ± SD. Comparisons were made using unpaired Student's t-test, and statistical significance was defined as P ≤ 0.05.

$$\text{Wound healing percentage} = \frac{\text{Initial wound area} - \text{Final wound area}}{\text{initial wound area}} \times 100$$

Results

Blood glucose

Based on the evaluation of blood glucose levels, a significant reduction was observed in the diabetic + PRP group compared with the diabetic group on day 3 of treatment (Pvalue≤0.05) (Figure 1). On day 12, no significant difference in glucose levels was detected between the two groups (Pvalue>0.05) (Figure 2). Similarly, on day 21, although the diabetic + PRP group showed lower glucose levels compared with the diabetic group, this difference was not statistically significant (Pvalue>0.05) (Figure 3). Overall, these findings suggest that PRP administration can induce a significant early reduction in blood glucose levels in the diabetic model; however, this effect was not maintained at later stages of treatment.

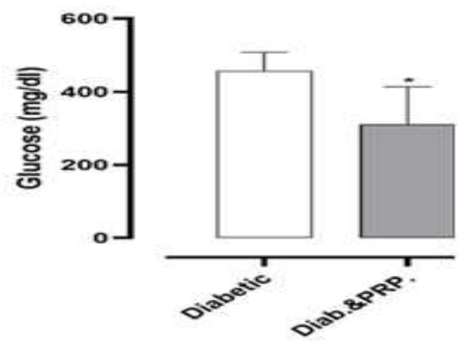

Figure 1: Blood glucose values (mean ± standard deviation) in the diabetes and diabetes + PRP groups on the third day of treatment. A significant decrease in blood glucose levels was observed in the diabetes + PRP group compared with the diabetes group (P<0.05).

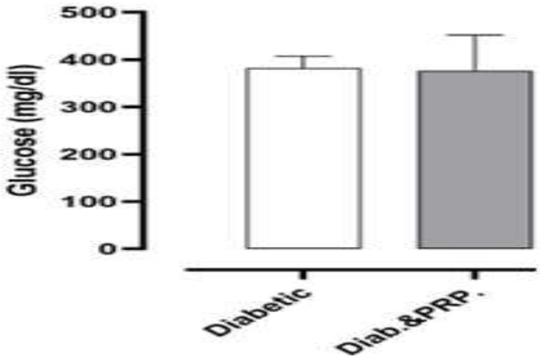

Figure 2: Blood glucose values (mean ± standard deviation) in the diabetes and diabetes + PRP groups on the twelfth day of treatment. No significant difference was observed between the diabetes + PRP group and the diabetes group (P>0.05).

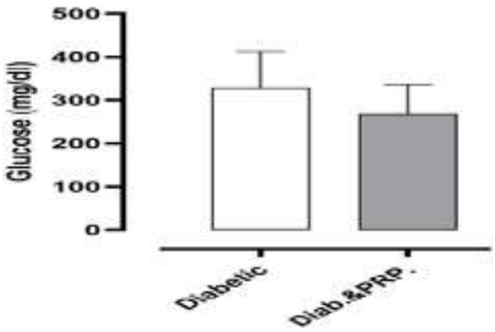

Figure 3: Blood glucose values in tail vein samples (mean ± standard deviation) in the diabetes and diabetes + PRP groups on the 21st day of treatment. No significant decrease was observed in the diabetes + PRP group compared with the diabetes group (P>0.05).

Interleukin-6 serum level

At the end of the treatment period (day 21) serum IL-6 levels were significantly higher in the diabetic group compared with the diabetic + PRP group (P≤0.05) (Figure 4-8). This finding indicates that PRP administration was associated with a marked reduction in systemic inflammation.

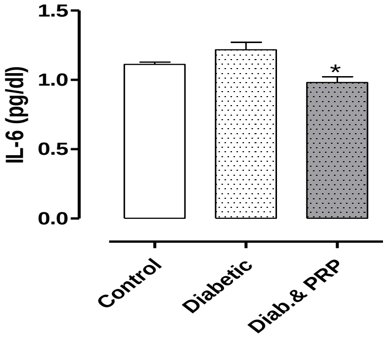

Figure 4: Serum values (mean ± standard deviation) interlukin-6 in control groups show diabetes, Diabetes + PRP on the 21st day of treatment. * It shows a significant difference in the diabetes group +PRP in the category with the diabetic group. (P<0.05)

TNF-α serum level

At the end of the treatment period (day 21) serum TNF-α levels showed a significant increase in the diabetic group compared with both control and diabetic + PRP groups (P≤0.05) (Figure 4-9). These findings suggest that PRP treatment was associated with a reduction of systemic inflammatory responses in the diabetic model.

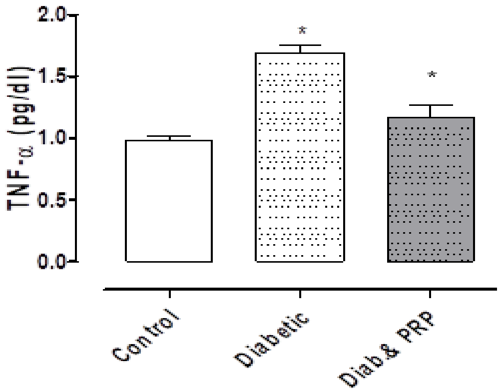

Figure 5: Serum values (mean ± standard deviation) TNF-α in control groups show diabetes, Diabetes + PRP on the 21st day of treatment. * It shows a significant difference in diabetic group with control and diabetes groups + PRP. (P<0.05)

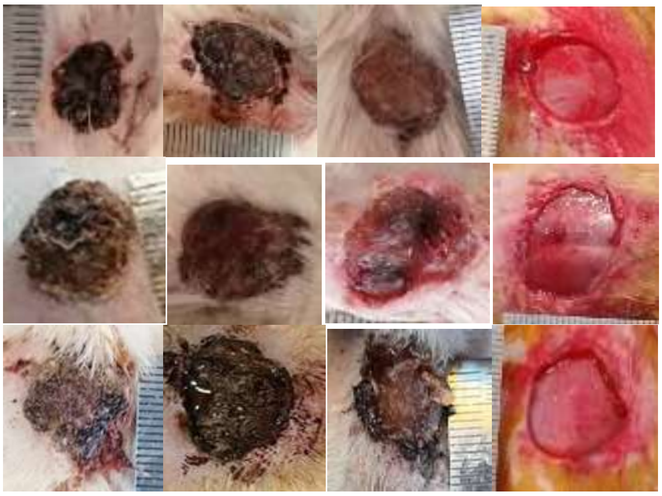

Figure 6: shows the wound healing process in different groups on days 3, 7, 12, and 21 after treatment. Macroscopically, the lack of wound healing in the diabetic group is clearly evident.

Discussion

Diabetes mellitus, as one of the most prevalent metabolic disorders, is not only characterized by chronic hyperglycemia but is also associated with a series of inflammatory and oxidative alterations that play a critical role in tissue injury and the development of chronic complications. Persistent hyperglycemia activates multiple molecular pathways, including excessive free radical production, polyol pathway activation, and accumulation of advanced glycation end products (AGEs), ultimately leading to pancreatic β-cell damage and insulin resistance (González et al, 2023). Oxidative stress and inflammation represent two interrelated mechanisms in the pathophysiology of diabetes that exacerbate each other. In chronic hyperglycemia, activation of metabolic pathways such as the polyol and hexosamine shunts, in addition to enhanced AGE formation, results in excessive generation of reactive oxygen species (ROS). Accumulated ROS not only damage proteins, DNA, and cellular membranes but also activate inflammatory signaling cascades, such as NF-KB, thereby upregulating pro-inflammatory cytokines including TNF-α and IL-6. These cytokines impair insulin signaling by inducing abnormal phosphorylation of insulin receptor substrates (IRS-1), reducing cellular insulin sensitivity, and exacerbating insulin resistance. Specifically, TNF-α in adipose tissue promotes lipolysis and free fatty acid release, while IL-6 in the liver enhances gluconeogenesis, both contributing to impaired glucose homeostasis (Weinberg Sibony et al, 2024).

Platelet-rich plasma (PRP), due to its high concentration of growth factors (e.g., PDGF, TGF-β, VEGF, and IGF-1) and regulatory cytokines, has emerged as a promising therapeutic approach for tissue regeneration and inflammatory modulation. Evidence suggests that PRP not only stimulates cellular repair but may also attenuate inflammatory responses and improve glucose metabolism, highlighting its potential in metabolic and inflammatory disorders such as diabetes (Cao et al, 2023; Zheng et al, 2023).

The present study demonstrated that PRP administration significantly reduced blood glucose levels in the diabetic animal model, particularly evident on days 3 and 21 of treatment. Moreover, inflammatory analyses indicated that TNF-α and IL-6, as central mediators of systemic inflammation, were significantly decreased in the diabetic group receiving PRP compared with untreated diabetic controls. These findings suggest that

PRP exerts dual benefits in diabetes by both improving glucose metabolism and attenuating inflammatory pathways.

The significance of the current research lies in providing experimental evidence of PRP's simultaneous anti-hyperglycemic and anti-inflammatory actions. These outcomes may pave the way for novel therapeutic strategies with fewer side effects for diabetic patients, underscoring the clinical potential of PRP in managing the metabolic and inflammatory complications of diabetes.

Supporting these findings, Ahmad et al. (2017) reported that autologous PRP gel promoted complete healing of diabetic wounds while reducing infection rates, offering strong clinical support for PRP application in diabetic care. The major similarity between their clinical study and the present research is the emphasis on PRP's modulatory and regenerative effects in diabetic conditions. While Ahmad's study highlighted clinical efficacy in wound repair, our findings expand this perspective by showing that PRP also reduces TNF-α and IL-6 levels and improves glycemic control in a diabetic animal model (Ahmed et al, 2017).

Gong et al. (2023) conducted a systematic review demonstrating that PRP use in patients with diabetic foot ulcers, compared to standard therapy, significantly accelerated wound healing and reduced infection risk. The central similarity with our study lies in the therapeutic and modulatory role of PRP in diabetes. However, a key distinction exists: Gong's study evaluated clinical outcomes in patients focusing primarily on wound healing, whereas our investigation employed an animal model and additionally assessed biochemical markers, specifically the reduction of IL-6 and TNF-α alongside improved glucose regulation.

Verts et al. (2020) further elucidated that variables such as platelet dosing, leukocyte content, and preparation techniques (e.g., centrifugation speed and duration) directly influence the biological efficacy of PRP in tissue repair, inflammation control, and immune modulation. Their review highlighted the mechanisms through which PRP regulates the inflammatory phase, stimulates angiogenesis, and creates a favorable environment for tissue regeneration.

Similarly, Menchisheva et al. (2019) identified PRP as an effective approach in facilitating wound repair, reporting decreased inflammatory markers and enhanced tissue regeneration. In particular, reductions in IL-6 and TNF-α levels were among the most notable findings.

Our current findings align with these reports by demonstrating significant reductions in IL-6 and TNF-α following PRP administration in a diabetic model. This consistency highlights the crucial role of PRP in inhibiting key cytokines that not only mediate inflammation but also exacerbate metabolic dysregulation in diabetes. Thus, PRP's anti-inflammatory and modulatory functions gain further importance in the context of complex pathophysiological conditions such as diabetes.

In summary, the present study provides strong experimental evidence that PRP exerts both anti-hyperglycemic and anti-inflammatory effects in a diabetic model, primarily through reducing pro-inflammatory cytokines TNF-α and IL-6 and improving glucose regulation. These findings, together with supporting clinical and review studies, highlight PRP as a promising adjunctive therapy for diabetes and its complications.

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Conflict of interest

The authors declare that they have no conflict of interest regarding the present study.

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اثر پلاسمای غنی از پلاکت (PRP) بر قند خون، سیتوکین‌های التهابی و ترمیم زخم در موش‌های صحرایی دیابتی

مریم بابایی[۱]، مسعود علیرضایی[۲]، معین یزدخواستی[۳]* و قاسم فرجانی کیش[۴]

[۱] دانش‌آموخته دکترای حرفه‌ای، دانشکده دامپزشکی، دانشگاه لرستان، خرم آباد، ایران
[۲] دانشیار گروه علوم پایه، دانشکده دامپزشکی، دانشگاه لرستان، خرم آباد، ایران
[۳] استادیار گروه علوم درمانگاهی، دانشکده دامپزشکی، دانشگاه لرستان، خرم آباد، ایران
[۴] دانشیار گروه پاتوبیولوژی، دانشکده دامپزشکی، دانشگاه لرستان، خرم آباد، ایران

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چکیده

دیابت ملیتوس یکی از شایع‌ترین اختلالات متابولیک است که نه تنها با هیپرگلیسمی پایدار بلکه با افزایش استرس اکسیداتیو و پاسخ‌های التهابی نیز شناخته می‌شود. در میان سیتوکین‌های پیش‌التهابی، فاکتور نکروز توموری-آلفا (TNF-α) و اینترلوکین-۶ (IL-6) نقش محوری در اختلال سیگنالینگ انسولین، افزایش لیپولیز و گلوکونئوژنز و تشدید دیس‌فانکشن متابولیک دارند. پلاسمای غنی از پلاکت (PRP)، که سرشار از فاکتورهای رشد و سیتوکین‌های تنظیمی است، اخیراً به عنوان یک راهبرد درمانی بالقوه برای بازسازی بافت و کنترل التهاب مورد توجه قرار گرفته است. در این مطالعه، دیابت در موش‌های صحرایی نژاد ویستار با استفاده از استرپتوزوتوسین (۶۵mg/kg) القا شد و زخم‌های تمام‌ضخامت به ابعاد ۲ سانتی‌متر در پشت حیوانات ایجاد گردید. گروه درمانی از روز ششم تا روز بیستم، به صورت روزانه، درمان موضعی با PRP اتولوگ (۵۰ واحد؛ ۱ میلی‌لیتر به ازای هر کیلوگرم وزن بدن) دریافت کردند. قند خون در فواصل مشخص پایش شد و غلظت سرمی IL-6 و TNF-α به روش ELISA اندازه‌گیری گردید. درمان با PRP موجب کاهش معنی‌دار سطح قند خون شد، به ویژه در روزهای سوم و بیست و یکم مداخله. علاوه بر این، TNF-α و IL-6 به عنوان دو سیتوکین کلیدی در التهاب سیستمیک، در گروه دیابتی درمان شده با PRP نسبت به گروه دیابتی بدون درمان به طور قابل توجهی کاهش یافتند. یافته‌ها شواهد آزمایشگاهی روشنی از خواص ضدهیپرگلیسمی و ضدالتهابی PRP در دیابت ارائه می‌دهند. با کاهش بیان IL-6 و TNF-α، PRP نه تنها متابولیسم گلوکز را بهبود می‌بخشد بلکه پاسخ‌های التهابی را نیز تعدیل می‌کند و پتانسیل آن را به عنوان یک درمان کمکی نوین در عوارض متابولیک و التهابی دیابت نشان می‌دهد.

کلمات کلیدی: دیابت ملیتوس، عوامل التهابی، گلوکز، PRP، موش صحرایی

* نویسنده مسئول: معین یزدخواستی، استادیار گروه علوم درمانگاهی، دانشکده دامپزشکی، دانشگاه لرستان، خرم آباد، ایران
E-mail: yazdkhasti.m@lu.ac.ir